Why does prenatal infection prime the brain for psychosis?

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I, Anjali Bhat, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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"It's not the strongest that survive, nor the most intelligent, but the most responsive to change."

— *Popular misquotation of Charles Darwin* [†]

[†]In fact, a paraphrase of a paraphrase by Leon C. Megginson, *Petroleum Management*, (1964).

Contents

Abstract

In this thesis, I interrogate the mechanisms of association between immune insults in prenatal development and psychotic disorders, with a particular focus on schizophrenia. Schizophrenia has been cast, from different neuroscientific perspectives, as a polygenic disorder, as a neurodevelopmental disorder and as a sensory processing disorder. The dysconnection hypothesis draws together these strands of research to construct a coherent picture of how schizophrenia may arise, specifically implicating a functional synaptopathy as the aetiological core of psychotic symptoms. One strand that has not yet been woven into this tapestry is the immune system, which has been overwhelmingly linked with psychosis in recent years. I set out to bridge these interpretations using a variety of methods, namely, statistical genetics, cell biology, electroencephalography and theoretical neurobiology. *Chapter 1* is a transcriptome-wide association study of the mismatch negativity (MMN), exploring the genetic underpinnings of sensory processing itself. The MMN is an electroencephalographic signature that is consistently altered in patients with psychosis. *Chapter 2* is a differential gene expression study of human neural progenitor cells stimulated *in vitro* with pro-inflammatory cytokines, showing suppressed transcriptional responses to inflammation in cells from people with schizophrenia. These findings are potentially important for the understanding of synaptic dysfunction in schizophrenia that may underwrite false inference of the kind associated with delusions and hallucinations. Finally, *Chapter 3* considers the immune system itself as performing an elementary kind of inference: immunoceptive inference. This offers a first principles account of the immune response that extends the reach of immunology in helping to understand psychiatric disorders, as well as a new way of understanding interactions between the immune system and the brain.

Impact Statement

The work presented in this thesis bridges cognitive neuroscience, psychiatric genetics, cell biology and theoretical neurobiology. Each of these fields have their own well-established bodies of literature on the aetiology of psychotic disorders, but so far have had minimal overlap. The first chapter addresses two major open questions. Firstly, it interrogates the biological mechanisms that underlie the computational model of psychosis as a disorder of 'aberrant precision'; to be able to understand this would have major consequences not only for the systems-level conceptualisation of psychosis, but potentially computational psychiatry as a whole, where the idea of the brain as a predictive organ predominates. It does so by identifying genes whose expression influences the mismatch negativity (MMN), a measure of prediction 'error'. We have assembled here, to my knowledge, the largest dataset of the MMN to date. This, as well as the recently developed transcriptome-wide association study approach used, has made it possible to conduct the first ever MMN genetic association study. Secondly, therefore, I am able to endorse the notion of the MMN as a psychosis endophenotype. MMN amplitude is reliably attenuated in people with psychosis and studying the genetics of a well-defined and objectively quantifiable measure like the MMN has strong potential to yield key insights into the biological mechanisms of psychosis development. However, an important criterion for a trait being a useful endophenotype is genetic overlap with the disease, which has not, until now, been possible to validate for the MMN.

The second chapter identifies new gene targets for future research on the influence of maternal immune activation on schizophrenia susceptibility and resilience. These findings exemplify differences in how the brains of people with schizophrenia may have responded to infection or inflammation during prenatal development and suggest immune insults early in life can alter neurotransmission – and therefore, potentially, the course of subsequent neurodevelopment. These findings are also potentially important for the understanding of synaptic dysfunction that may underwrite hallucinations and delusions in schizophrenia. Finally, the third chapter offers a first principles account of the immune response that

extends the reach of immunology in helping to understand psychiatric disorders, as well as a new way of understanding interactions between the immune system and the brain. These formulations demonstrate the benefit of a surrender of mind-body and brain-body dualisms that may be of particular importance to psychiatric practice, where it encourages a holistic treatment of patients. For example, with an embodied perspective on the mind, a patient presenting with psychosis is more likely to be treated with reference to the mechanisms leading to this syndromic endpoint, whether that be schizophrenia (managed with antipsychotics), or an alternative diagnosis such as Cushing's syndrome, which can be effectively treated by normalising cortisol levels. Furthermore, this embodied perspective is fundamental to progressing the understanding of psychotropic drugs; for example, why muscle relaxants such as benzodiazepines reduce anxiety.

Publications directly associated with the work in this thesis:

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3. Thygesen, J. H., Presman, A., Harju-Seppänen, J., Irizar, H., Jones, R., Kuchenbaecker, K., . . . Bramon, E. (2020). Genetic copy number variants, cognition and psychosis: a meta-analysis and a family study. *Molecular Psychiatry*. doi:10.1038/s41380-020-0820-7
4. Calafato, M. S., Austin-Zimmerman, I., Thygesen, J. H., Sairam, M., Metastasio, A., Marston, L., . . . Bramon, E. (2020). The effect of CYP2D6 variation on antipsychotic-induced hyperprolactinaemia: a systematic review and meta-analysis. *Pharmacogenomics J, 20*(5), 629-637. doi:10.1038/s41397-019-0142-9

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Introduction

Schizophrenia and psychosis

Schizophrenia is a devastating mental illness that affects over twenty million people worldwide (Disease and Injury Incidence and Prevalence Collaborators, 2018). Its most distinguishing symptom is psychosis[2], which usually occurs in episodes: some individuals experience a single episode, while others experience multiple episodes over the course of their lives (American Psychiatric Association, 2013). Psychosis is characterised by hallucinations (percepts that do not correspond with 'reality'[3]) without insight, and delusions (strongly held beliefs that, again, do not correspond with reality). Importantly, these hallucinations and delusions are usually persecutory in nature, which is one of the things that makes this a particularly distressing illness: the most common psychotic hallucinations involve 'hearing voices' that are often threatening or critical[4] (Nayani & David, 1996; Thorup et al., 2007), and the most common delusions involve paranoia about, for example, being followed or poisoned (American Psychiatric Association, 2013; Nayani & David, 1996). In addition, a range of other (non-episodic) symptoms may be observed in patients with schizophrenia; for example, confused thoughts, cognitive deficits, low motivation and difficulties with concentration (American Psychiatric Association, 2013). There are effective antipsychotic medications that can alleviate some of these symptoms – albeit with common and potentially serious side effects (Lally & MacCabe, 2015; Rummel-Kluge et al., 2010). However, a mechanistic understanding of why these medications work (when they do), and indeed what causes psychosis, is largely elusive: why *does* a dopamine receptor antagonist make a person less likely to hear malevolent voices?

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[2] Psychosis can also occur as a symptom of other neuropsychiatric disorders such as bipolar disorder or major depression.

[3] 'Reality' in this diagnostic criterion implicitly refers to 'objective' percepts as agreed upon by a majority of observers.

[4] Although, interestingly, the nature of the voices may be highly dependent upon cultural influences (Luhrmann et al., 2015).

What is clear is that schizophrenia is a hugely multi-faceted disorder: it has a significant genetic component (Brainstorm Consortium, 2018; Hilker et al., 2018; Pardiñas et al., 2018); there are associated cognitive deficits in, for example, working memory (J. H. Thygesen et al., 2020) and well-established electrophysiological correlates (Bramon et al., 2004; Bramon et al., 2005; Erickson et al., 2016; Naatanen et al., 2012; Shelley et al., 1991); there are strongly-associated pharmacological risk factors such as cannabis use (D'Souza et al., 2005; Hajos et al., 2008; van Os et al., 2008); there are several links with autoimmune disorders and infection (Benros et al., 2011); and, of course, there is a neurodevelopmental factor, which is still not well understood (Insel, 2010). What we are currently in need of is a way to integrate these lines of evidence into a coherent aetiology.

Schizophrenia as a genetic disorder

Schizophrenia has been estimated to have a heritability as high as 60-80% (Bergen et al., 2012; Brainstorm Consortium, 2018; Hilker et al., 2018) and has a well-established polygenic profile: a seminal genome-wide association study (GWAS) by the Psychiatric Genetics Consortium (PGC) linked 108 genetic loci with the disorder in a large cohort of European ancestry (Schizophrenia Working Group of the Psychiatric Genomics, 2014). A more recent study found 19 schizophrenia-associated loci in a large East Asian sample, with effects of common genetic variants that were highly similar to the European ancestry cohorts, suggesting that the biology of schizophrenia is shared between populations (Lam et al., 2019). Each of these loci, or single nucleotide polymorphisms (SNPs), have small odds ratios individually (generally less than 1.2) for the risk of developing schizophrenia, but collectively contribute considerably to the variance in liability (Bray & Hill, 2016). However, many of these loci are in non-coding regions of the genome, which has made it challenging to interpret how variants at these loci elicit psychopathology (Hall, Pain, et al., 2020; Schizophrenia Working Group of the Psychiatric Genomics,

2014). It is likely that many of these variants are, rather, regulatory elements that influence genes at a distance (Bray & Hill, 2016; Gusev et al., 2018).

Translating these genetic associations into molecular mechanisms requires, first and foremost, an understanding of which genes are impacted by the variants; and how, when and where these effects transpire (Bray & Hill, 2016; Gusev et al., 2018; Hall, Pain, et al., 2020). A recent update from the PGC with an even larger European ancestry sample has been released as a preprint, showing genome-wide significant associations with 270 loci (Ripke et al., 2020) and enrichment for genes involved in synaptic biology, including the glutamate receptor subunit gene *GRIN2A.*

In addition to these common risk variants that collectively contribute to schizophrenia risk, there are also a number of rare risk variants (present in <1% of the general population) and *de novo* mutations that are known to contribute as well (Flint, 2016; Marshall et al., 2017; Singh et al., 2016; Singh et al., 2017). These rare variants often carry much higher odds ratios for schizophrenia risk (Bray & O'Donovan, 2019; Flint, 2016), as evidenced by exome sequencing studies (Schizophrenia Exome Meta-Analysis (SCHEMA) Consortium et al., 2020; Singh et al., 2016; Singh et al., 2017) and copy number variants (CNVs), which are deletions, duplications or insertions of large sequences of DNA (>1 kb) (Marshall et al., 2017). Indeed rare CNVs appear twice as frequently in genomes of people with schizophrenia than those of the general population (Bray & O'Donovan, 2019). Moreover, one of the highest risk groups are people with DiGeorge syndrome (a.k.a. velocardiofacial syndrome) who bear a CNV in the 11.2 region of chromosome 22. Individuals with this congenital disorder are ~30 times more likely to develop schizophrenia than the general population (Charlson et al., 2018; Murphy et al., 1999); and although 22q11.2 deletion occurs in only 1 out of every 4000 live births, it is present in around 1 in 100 people with schizophrenia (Scambler, 2000). This tends to be a very large deletion (~1.5-3 Mb) which omits at least 40 protein-coding genes and has systemic effects (e.g., on cognition, immunity, endocrinology, heart and lung function). Many of these genes are highly expressed in the brain and are

involved in cortical development and neuronal migration (Jonas et al., 2014). A seminal study by Marshall et al (2017) showed across a sample of 41,321 subjects that CNV 'burden' (the extent of copy number variation across the genome) significantly contributes to schizophrenia risk. Exome sequencing studies that search large samples for rare variation at the SNP level amidst protein-coding genes also show that patients with schizophrenia exhibit a high burden of these rare variants – particularly those causing loss of function of *SETD1A*, which encodes a histone modifier (Singh et al., 2016; Singh et al., 2017). A recent preprint that uses exome sequencing further identifies rare coding variants in 10 genes which confer significant risk for schizophrenia (Schizophrenia Exome Meta-Analysis (SCHEMA) Consortium et al., 2020).

A key approach to further elucidating the mechanisms by which these genes influence disease risk are studies of gene *expression*: the extent to which the genetic 'blueprint' (DNA) is transcribed and translated to produce proteins. There is an additional level of nuance that can be captured at this level, as the expression of a gene is influenced bidirectionally by the DNA sequence that encodes it (and any genomic elements regulating it), as well as the environmental influences that may suppress or enhance it (Boyce et al., 2020).

An accepted way of inferring the level of transcription of a gene is to count the RNA 'reads' corresponding to that gene at a given time-point – traditionally averaged across cells in a tissue sample, though single-cell RNA sequencing is now possible (Shapiro et al., 2013). Gene expression studies have, in the past, only been possible in relatively small samples and by analysing individual genes, usually using animal models or post-mortem tissue (Bray & Hill, 2016; Gusev et al., 2018; Warre-Cornish et al., 2020). However, novel methods such as transcriptome-wide association studies (Chapter 1) have made possible genome-wide profiling of gene expression in much larger cohorts – which has already been fruitfully leveraged to yield mechanistic insights, such as the relevance of chromatin activity to the development of schizophrenia (Gusev et al., 2018; Hall, Medway, et al., 2020). Differential gene

expression analysis in human *in vitro* neural networks has now also been made possible due to recent advances in stem cell biology (Chapter 2) (Brennand & Gage, 2011; Takahashi & Yamanaka, 2006). At this stage of schizophrenia research, therefore, gene expression studies offer one of the most relevant molecular approaches to elucidating the pathophysiology of the disorder.

These advances are promising for the current paradigm-shifting struggle in psychiatry to integrate a symptom-based[5] classification of mental disorders with advances in genetic and neuroscientific research on psychopathology (Carcone & Ruocco, 2017; Insel, 2010). An important way of addressing this struggle – in the field of psychiatric genetics – has been to identify endophenotypes for psychiatric disorders. An endophenotype is a well-characterised behavioural or physiological measure – ideally a response measure such as an event-related potential – that sits between genetic aetiology and the phenomenology of a disorder (Gottesman & Gould, 2003; Iacono et al., 2017; Insel & Cuthbert, 2009). In essence, identifying these intermediate phenotypes is an attempt to understand the mechanisms by which genetic variants influence a phenotype, and to stratify a heterogeneous, polygenic disease classification by associating a subset of genetic influences with a subset of symptoms or characteristics. Such stratification may also make it easier to study schizophrenia in model systems (can a mouse be schizophrenic?) by setting the more achievable goal of modelling specific endophenotypes for the disorder and/or examining the impact of genes that GWASs and gene expression studies have associated them with.

Schizophrenia as a sensory processing disorder

From a computational perspective, psychosis has also been conceptualised as a disorder of aberrant salience or sensory precision (Kapur, 2003; Limongi et al., 2018). This account comes from the notion

[5] In many cases externally observed rather than phenomenological (American Psychiatric Association, 2013)

of 'predictive coding' in the brain, which considers the brain as a statistical organ that maintains a model of its environment that generates predictions, compares them to sensory input and updates itself to minimise discrepancies (or prediction 'errors') (Helmholtz, 1866/1962; Knill & Pouget, 2004). In other words, the brain is not just passively taking in sensory information at any given moment, but also integrating it with previous experience – such that our experiences are not carbon copies of the external world but rather coloured by what our brains deem most *likely* to be true. The term 'belief' is taken from probability theory, in the sense of Bayesian beliefs: it applies to any sort of interaction between a brain[6] and its environment – even at the most fundamental, reflexive levels. Crucially, this kind of (Bayesian) belief updating depends upon the relative precision of prior beliefs and sensory evidence; 'precision' being a measure of predictability or certainty (or, strictly speaking, inverse variance of a distribution over a belief). If sensory data are imprecise (e.g., as with a blurred image), prior beliefs are less likely to be updated. That said, it is important to note that the precisions themselves are also being predicted (i.e., high order predictions of predictability): different individuals may have different thresholds of relative precision at which they will update a particular belief. An intuitive analogy for this Bayes optimal precision weighting could be a scientist ascribing certainty (e.g., signal-to-noise) to experimental data and weighing these data against an existing body of prior knowledge, to decide whether to accept or reject the hypothesis at hand (Parr & Friston, 2019).

The hierarchical organisation of the brain is particularly important for predictive coding in the brain. 'Bottom-up' prediction errors – elicited by signals from sensory receptors – are thought to be passed up cortical hierarchies, wherein 'higher levels' of the cortex contextualise prediction errors that are passed up from 'lower' levels. Prediction errors that cannot be resolved at a particular level are passed up; each upward progression corresponding to higher degrees of abstraction and likelihood of conscious

[6] Indeed, any organism and its environment. This idea will be expanded upon in Chapter 3.

control (R. A. Adams et al., 2013; Benrimoh et al., 2019; Limongi et al., 2018). In psychosis, the precision-weighting of sensory stimuli and prior beliefs is generally thought to be off-kilter (Limongi et al., 2018). This is supported by the fact that patients with psychosis consistently show significantly smaller mismatch negativity (MMN) than healthy controls (Erickson et al., 2016; Naatanen et al., 2012; Shelley et al., 1991): the MMN is an electroencephalographic signature thought to be representative of prediction 'error' (Chapter 3). Here, prior beliefs may be 'overweighted' in hallucinations (as in, perception can even occur in the absence of any incoming sensory information) and 'underweighted' in the case of illusions (schizophrenic individuals are often more resilient to certain illusions than controls): an inconsistency that, it has been suggested, can be better understood in a hierarchical context (Benrimoh et al., 2019; Brown et al., 2013; Powers et al., 2017). The current account, put forward by the dysconnection hypothesis (unpacked in detail below), is that people with psychosis hold overly precise prior beliefs (as may be the case with delusions) as a compensation for a failure of 'sensory attenuation', which is, heuristically, the ability to ignore sensory stimuli. Sensory attenuation is particularly important for sensations that are elicited by self-generated actions[7] to protect predictions of an intended movement from revision by ascending prediction errors. Failures of sensory attenuation, which create uncertainty about control over an action, have been associated with misattribution of agency as seen in psychosis: it appears that people with psychosis may 'explain away' this uncertainty by assuming their actions are under the control of another (R. A. Adams et al., 2013; Brown et al., 2013; Parees et al., 2014).

However, the synaptic and molecular mechanisms by which predictive coding is realised in the brain are still unclear. To understand this would have major consequences not only for the systems-level

[7] In healthy subjects sensory attenuation has been demonstrated by the inability to tickle oneself (Blakemore et al., 2000; Van Doorn et al., 2014).

conceptualisation of psychosis, but potentially computational psychiatry as a whole, where the idea of the brain as a predictive organ predominates.

Schizophrenia as an immune disorder

Prenatal exposure to infection is a significant risk factor for schizophrenia (Byrne et al., 2007; Estes & McAllister, 2016; Kepinska et al., 2020; Meyer, 2019; Warre-Cornish et al., 2020). This notion gained traction in the 1990s, when epidemiological studies increasingly identified season of birth as a major risk factor (Jablensky, 1995; Torrey et al., 1997): babies born in Winter or Spring appeared to have a significantly increased risk of developing psychosis later in life (Brown, 2006; Smith et al., 2007). Eventually, the finding was interpreted to reflect the fact that Winter or Spring birth would mean a coincidence of early- to mid-pregnancy with influenza season (Brown, 2006; Brown et al., 2004; Kunugi et al., 1995; Mednick et al., 1988; Sham et al., 1992). A retrospective study of archived maternal serum samples indeed found that presence of influenza antibodies in early- to mid- pregnancy sera increased the probability of schizophrenia in offspring 7-fold (Brown et al., 2004).

However, it emerged that this effect of prenatal exposure to infection is not restricted to the influenza virus: a similar effect has been seen, for example, with bacterial infections such as pneumonia and tonsilitis; as well as the parasite *Toxoplasma gondii* (Estes & McAllister, 2016; Knuesel et al., 2014; Patterson, 2009). Nor is elevated risk due to infection unique to schizophrenia: prenatal infection has also been linked to other neuropsychiatric conditions such as autism (Brown & Meyer, 2018; Estes & McAllister, 2016; Patterson, 2009) and bipolar disorder (Canetta et al., 2014). This began to suggest that it may not be specific antigens that increase the risk of schizophrenia, but rather the immune responses that they trigger (Estes & McAllister, 2016; Kepinska et al., 2020; Meyer, 2019). Subsequent studies in animal models of prenatal development indeed showed that induction of the maternal immune response, in the absence of infection, resulted in phenotypes characteristic of schizophrenia, such as attenuated pre-

pulse inhibition as well as working memory and synaptic deficits (Meyer, 2014, 2019). Post-mortem transcriptomic studies of brain tissue from patients with schizophrenia have shown significant enrichment for genes involved in regulating the immune response (Gandal et al., 2018). This is also supported by the significant overlap between several autoimmune disorders and schizophrenia; for example, systemic lupus erythematosus, psoriasis and rheumatoid arthritis (Chen et al., 2019; Tiosano et al., 2017; Ungprasert et al., 2019). Indeed, some accounts even suggest that schizophrenia *is* an autoimmune disorder (Adams et al., 2012; Knight et al., 1992).

Genetic association studies have also revealed genes involved in immune pathways to be some of the most significant schizophrenia risk factors; most notably, genes within the major histocompatibility complex (MHC) regions of the genome, such as the human leukocyte antigen (*HLA*) genes (Marshall et al., 2017; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Wright et al., 2001) and the gene encoding complement component C4A[8] (Sekar et al., 2016). This last is a landmark study that uses multiple techniques in addition to genetic association to thoroughly implicate C4A expression in the development of schizophrenia. Sekar et al. (2016) further suggest a potential mechanism by which C4A confers risk for schizophrenia: stimulation of excessive synaptic pruning. They first show, using immunocytochemistry of post-mortem prefrontal and hippocampal tissue, that C4A is present at synapses. They then go on to demonstrate that C4A deficient mice exhibit defects in synapse remodelling. It has long been speculated that the cortical synaptic pruning that typically occurs during adolescence and early adulthood may be of particular relevance to schizophrenia, given that this period is also when schizophrenia tends to become clinically apparent (Feinberg, 1982). (Please see 'The synaptic pruning hypothesis', below, for more detail). Complement receptors in the brain are

[8] *HLA* genes encode components of important antigen-presenting proteins on immune cell surfaces; complement components are part of a complex molecular cascade involved in the innate immune response – as further detailed in Chapter 3.

predominantly expressed by immunity-mediating microglial cells that facilitate pruning of redundant or dysfunctional synapses (Lee et al., 2014), which leads Sekar et al. (2016) to put forward the possibility that excessive synaptic pruning by microglial phagocytosis – stimulated by the complement cascade – causes schizophrenia symptoms to surface during adolescence/early adulthood. This hypothesis has been further supported by a more recent study which showed, using *in vitro* microglial-neuronal cultures derived from human cells, that schizophrenia cell lines exhibit increased synaptic elimination by microglia (Sellgren et al., 2019). This study also found that the presence of schizophrenia-related risk variants at the *C4* locus contributed at least in part to this increased synaptic pruning. As we will see in the next section, this interaction between immunity and synaptic function is a recurring theme that is of central importance to this thesis and may be concurrently necessary for the emergence of psychosis.

Core aetiology

Given the many factors that contribute to the development of schizophrenia, a key imperative is to identify a core aetiology that they converge upon, without which a person would not experience symptoms such as psychosis. For intuition, this is analogous to asking who holds the smoking gun in a murder mystery, whilst simultaneously recognising that several people share some degree of responsibility for creating the circumstances that lead to the outcome (e.g., by stoking animosity or manufacturing the weapon). There are several theories as to what the core aetiology of schizophrenia may be. Here, I outline five of the leading hypotheses currently in circulation. The first two consider schizophrenia as a neurochemical disorder; the third considers schizophrenia a disorder of excessive synaptic pruning; the fourth considers schizophrenia a predominantly neurodevelopmental disorder; the fifth weaves all of these considerations together, framing schizophrenia as a disorder of synaptic dysconnection.

The dopamine hypothesis

The dopamine hypothesis of schizophrenia is a long-standing theory that the neurotransmitter dopamine lies at the heart of schizophrenia symptoms (Howes & Kapur, 2009). Three observations were particularly influential in the emergence of this hypothesis. First, that antipsychotic medications target dopaminergic D_2 receptors (Carlsson & Lindqvist, 1963), blocking neuronal reuptake of dopamine (Lally & MacCabe, 2015). Second, that their clinical efficacy is dependent upon their affinity for these receptors (Seeman & Lee, 1975). Third, that high doses of psychostimulant drugs (that increase dopamine levels in synaptic clefts) can induce psychosis (Lieberman et al., 1987). Given these observations, the original dopamine hypothesis posited that the core aetiology of schizophrenia is hyperdopaminergia, or, more specifically, an excess of dopamine uptake by neurons (Matthysse, 1973; Snyder, 1976).

There were, however, some shortcomings with this general story. For example, it became evident that serum dopamine levels were not universally elevated in patients with psychosis – and that dopamine receptors were not uniformly distributed around the brain (Davis et al., 1991; Howes & Kapur, 2009). Concurrently, Positron Emission Tomography (PET) studies began to show 'hypofrontality' (reduced blood flow to the frontal cortex) in patients with schizophrenia, which directly correlated with dopamine levels in cerebrospinal fluid (Howes & Kapur, 2009). 'Version II' of the dopamine hypothesis therefore differentiated between brain regions, suggesting that schizophrenic brains were characterised by hyperdopaminergia in the midbrain but hypodopaminergia in the prefrontal cortex (Davis et al., 1991).

Shortly after this, the literature around "schizophrenia and dopamine" burgeoned: over 6700 articles were published on the topic between 1991 and 2009. In particular, a gamut of genetic studies appeared, many associating dopamine-related genes such as *AKT* and *COMT* with schizophrenia (Arguello & Gogos, 2008). Around the same time, Kapur (2003)'s influential account of psychosis as a result of "aberrant salience" was published, which recognised the increasingly evident role of dopaminergic neurons in differentiating salient stimuli from noise. On the basis of these ideas, Howes

and Kapur (2009) therefore posited a further updated 'Version III' of the dopamine hypothesis that suggested that multiple 'hits' (e.g., genes, stress, drug exposure) combined to elicit dopamine dysregulation as seen in psychosis. Importantly, this version of the hypothesis emphasised dysregulation of dopamine transmission across synapses, as opposed to overall reduction in dopamine levels across tissues or brain structures. They further suggested that dopamine receptor-targeting antipsychotic drugs work downstream of the primary dopamine dysregulation, acting as an effective 'band-aid' in the short run, but perhaps worsening the primary dysfunction in the long run (leading to the rapid relapses often seen in psychosis patients who come off their medication).

The dopamine hypothesis has been highly influential, but a number of limitations have emerged that make it evident that dopamine alone cannot tell the whole story. Firstly, while dysfunction in dopamine transmission may induce psychosis, it does not account for the 'negative' symptoms (e.g., lethargy and flat affect) or 'cognitive' symptoms (e.g., deficits in working memory) of schizophrenia (Uno & Coyle, 2019; Yui et al., 2000). Antipsychotics (with the possible exception of clozapine) also do not tend to address these non-psychotic symptoms. Secondly, although first generation antipsychotics bind to dopamine receptors and reduce dopamine levels on the order of minutes, changes in symptoms are generally slow to follow (on the order of days) (Sonne et al., 2021; Takano et al., 2004). This suggests that psychotic symptoms may not be *directly* dependent upon dopamine transmission. Furthermore, there has been concurrently emerging evidence for other neurochemical hypotheses of schizophrenia, such as the glutamate hypothesis, which is overviewed below.

The glutamate hypothesis

As with the dopamine hypothesis, the glutamate hypothesis of schizophrenia emerged from pharmacological interactions with psychotic phenomenology. In this case, it became increasingly evident that drugs that target the glutamatergic N-methyl D-aspartate receptor (NMDA-R), such as

phenylcyclidine (PCP) and ketamine, can temporarily induce schizophrenia symptoms (Beck et al., 2020; Schmidt et al., 2013). Rather compellingly, these drugs induce not only psychosis but also the negative and cognitive symptoms, for as long as two weeks after administration (Coyle, 1996; Javitt & Zukin, 1991; Snyder, 1980). Indeed, Snyder (1980) observed that experienced psychiatrists assessing patients with a history of PCP use often mistook them for patients with schizophrenia (before their drug history was made available). Additionally, if patients with schizophrenia are given ketamine, their symptoms temporarily increase in severity (Malhotra et al., 1997).

Ketamine and PCP studies therefore began to strongly implicate their primary target, the NMDA receptor, in the aetiology of schizophrenia. This was further supported by the presentation of the autoimmune disease NMDA-R encephalitis wherein autoantibodies target a component of the NMDA-R, resulting in symptoms highly resemblant of schizophrenia (Warren et al., 2018; Zandi et al., 2011). Genetic studies have also overwhelmingly linked schizophrenia with glutamateric neurotransmission-related genes – in particular, the NMDA-R subunits *GRIN2A*, *GRIN2C* and *GRIN2D* (Ripke et al., 2020; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Yu et al., 2018) have led to the 'glutamate hypothesis', which suggests that the core aetiology of schizophrenia is a dysfunction in glutamate neurotransmission (Hu et al., 2015; Uno & Coyle, 2019). This more recent neurochemical hypothesis of schizophrenia is still prevalent, although it has been proposed that the effects of dopamine and serotonin on psychotic symptoms cannot be ignored – rather, that there is an integration of effects upon the pathways these three neurotransmitters are involved in that elicit the symptoms of schizophrenia (Stahl, 2018). Furthermore, to understand schizophrenia purely on the neurochemical level potentially omits important and consistent observations on other spatial and temporal scales. Indeed, there have been two other equally influential theories of schizophrenia aetiology that instead emphasise synaptic pruning and neurodevelopment, respectively. These are overviewed below.

The synaptic pruning hypothesis

Between birth and adulthood, the number of neurons in the brain reduces by approximately 15 percent (Sakai, 2020). Similarly, the number of connections between neurons tends to progressively reduce over the lifespan as well: the circuits that are relevant to survival in the environment a person occupies are prioritised, while those that are irrelevant are pruned away ("Use it or lose it", as the saying goes) (Shors et al., 2012). This pruning is particularly extensive in humans – and continues into relatively late in life compared to other species – and is considered to be key to our adaptability to a wide range of environments (Buckner & Krienen, 2013). There is a particularly concentrated flurry of pruning of these synaptic connections during adolescence and early adulthood (Feinberg, 1982). This also happens to be the period around which schizophrenia is characteristically diagnosed, leading some researchers to speculate whether there may be aberrant synaptic pruning in the brains of people with schizophrenia, that particularly comes to the fore during adolescence and early adulthood (Sakai, 2020). People with schizophrenia do indeed show abnormal cortical 'thinning' and synapse loss in neuroimaging and post-mortem studies (Keshavan et al., 2020; Sakai, 2020).

The current understanding of the synaptic pruning hypothesis has been significantly influenced by (Sekar et al., 2016)'s study showing the involvement of the complement gene *C4* in schizophrenia and synaptic pruning (Keshavan et al., 2020). As outlined above, this study showed that genetic variants that elicit higher expression of complement component C4 are related to schizophrenia. Furthermore, C4 was most highly expressed by microglia, which it had previously been suggested are involved in pruning of redundant neuronal synapses (Weinhard et al., 2018). This was expanded upon recently by Sellgren et al. (2019), who demonstrated engulfment of neuronal synapses by microglia – augmented in cells derived from patients with schizophrenia – as well as a direct relationship between the *C4* variants Sekar et al (2016) identified and this heightened synaptic elimination. They also examined long-term medical records to assess whether adolescents exposed to the tetracycline antibiotics doxycycline and

minocycline (prescribed for acne) were less likely to develop psychosis. They found that this was indeed the case with exposure to these tetracyclines (albeit moderately so) and not so with exposure to non-tetracycline antibiotics. This is particularly interesting because they further showed, *in vitro*, that tetracycline antibiotics reduce microglial phagocytosis of neuronal synapses in a dose-dependent fashion. In other words, the same medications that reduce synaptic pruning by microglia also moderately but significantly reduce the risk of psychosis onset.

Despite this compelling evidence, there are a few hurdles presented to the synaptic pruning hypothesis as well. The first is specificity: brains of people with schizophrenia show abnormalities in other cellular domains such as myelination and endothelia; complement variation and excessive pruning is not specific to schizophrenia (it is also implicated, for example in Alzheimer's disease); dendritic spine loss has been demonstrated only in deeper layers of the cortex (Keshavan et al., 2020). We are also still in need of more studies demonstrating excessive pruning in schizophrenia in real-time. Most of all, we are still in early stages of integrating these observations of immune-mediated synaptic pruning with findings supporting the neurochemical hypotheses of schizophrenia. That said, the synaptic pruning hypothesis is an integral component of a broader hypothesis of schizophrenia as a neurodevelopmental disorder.

The neurodevelopmental hypothesis

Emil Kraepelin's early description of 'dementia praecox' (Kraepelin, 1919), now called schizophrenia, characterised the disorder as an adult-onset neurodegenerative disease. When it was found that patients with schizophrenia have enlarged lateral brain ventricles and deficits in cognition, this was interpreted as confirmation of the neurodegeneration hypothesis (Johnstone et al., 1978). However, a seminal twin study later showed that patients with schizophrenia had larger ventricles than their monozygotic twin, suggesting an environmental contribution to the ventricular enlargement (Reveley et al., 1982). Studies

showing complications in prenatal development and maternal infection as risk factors of schizophrenia were also emerging (Murray et al., 1985). These developments led to two groups independently proposing a 'neurodevelopmental hypothesis' of schizophrenia (Murray & Lewis, 1987; Weinberger, 1987).

Since then, this has been backed by cohort studies found that early cognitive and motivational symptoms seen as early as eight years of age can predict schizophrenia later in life (Jones et al., 1994; Reichenberg et al., 2010). Further evidence for both environmental factors – such as childhood adversity (Matheson et al., 2013) and cannabis use (D'Souza et al., 2005) – and genetic contributors (Marshall et al., 2017; Murray et al., 1986; Pardiñas et al., 2018; Psychosis Endophenotypes International Consortium et al., 2014; Ripke et al., 2020) to psychosis risk also accumulated, leading to a 'two-hit' model of cumulative risk over neurodevelopment. In essence, this 'two-hit' theory suggests that a combination of genetic risk and environmental insult is necessary to alter neurodevelopment to the point that schizophrenia symptoms become clinically apparent (Feigenson et al., 2014; van Os et al., 2008).

The most recent and perhaps most convincing evidence for the neurodevelopmental hypothesis, however, comes from studies of synaptic pruning and cortical thickness. Cannon et al. (2015) conducted an extensive multi-site, longitudinal neuroimaging study which showed that cortical thickness progressively reduces as patients develop psychosis. Psychosis usually manifests in late adolescence or early adulthood, when the frontal cortex is still developing (American Psychiatric Association, 2013; Insel, 2010). While the reasons for this characteristic age of onset is not yet fully understood, it has been observed (as mentioned above) that this corresponds to a critical period for synaptic pruning (Feinberg, 1982), and there is increasing evidence for the relevance of synaptic pruning – especially in the frontal cortex – to the aetiology of schizophrenia (Sakai, 2020; Sekar et al., 2016; Sellgren et al., 2019). Interestingly, this is a critical period for the formation of concepts of self, other, and their interrelation, which also tend to be distorted in schizophrenia, and have also been linked to frontal cortical pruning (R.

A. Adams et al., 2013; Blakemore & Choudhury, 2006; Brown et al., 2013; Burnett et al., 2011; Kilford et al., 2016). The general consensus at this point is indeed that schizophrenia is a neurodevelopmental disorder (Insel, 2010).

The dysconnection hypothesis

The dysconnection hypothesis (Friston et al., 2016; Friston & Frith, 1995; Stephan et al., 2009) attempts to draw together many of these hypotheses and varied strands of research to create a coherent picture of how schizophrenia arises. It posits that schizophrenia is a result of a failure of functional integration in the brain, specifying that the core pathophysiology of the disorder is aberrant synaptic gain control[9]. This is distinct from an anatomical disconnection syndrome, or a 'cutting of the wires'; rather, the idea here is that the processes that are causally affected in schizophrenia are governed by neurotransmitters that regulate communication between synapses. There are two key lines of evidence that this theory is based upon. The first is the convergence of literature from genetics, psychopharmacology and other fields upon disruption of the glutamatergic NMDA receptor in schizophrenia, licensing the suggestion that interactions between NMDA-Rs and other neurotransmitters are causally responsible for psychotic symptoms. The second is the possibility of temporarily inducing psychotic symptoms in healthy adults without abnormal neurodevelopmental trajectories or anatomical lesions, by administering

[9] Synaptic 'gain control' refers to the modulation of responsiveness of a (post-synaptic) neuron to input (Ranlund et al., 2016). In this thesis, this may be used interchangeably with 'neuromodulation' (Katz et al., 1994; Moran et al., 2013). These processes are highly related to 'synaptic efficacy', which is the ability of a presynaptic neuron to influence a post-synaptic neuron (Friston, 2005). All of these processes depend heavily on 'neurotransmission', which (in computational literature) may be used interchangeably with neuronal 'message passing' (Lawson et al., 2014; Parr et al., 2019). All of these terms broadly refer to communication between neurons. Aberrances in synaptic gain control may be referred to as 'synaptopathies'.

psychomimetic drugs such as ketamine, which dysregulate neurotransmission and even disrupt the mismatch negativity (Beck et al., 2020; Schmidt et al., 2013).

Friston et al. (2016) take a multi-tiered approach to contextualising the current evidence. They propose that a) the SNPs that have been associated with schizophrenia must directly or indirectly influence synaptic gain control (as has now been backed up by the most recent PGC paper (Ripke et al., 2020)); b) This influence is likely exerted on a molecular level via the NMDA receptor, which responds abnormally to the activity of neurotransmitters such as dopamine in psychosis; c) Structural changes at a cellular level and in neuroimaging of patients with psychosis are a result of activity-dependent pruning (which may also explain the cognitive deficits seen in schizophrenia); d) At the level of neural networks, altered synaptic gain control manifests as aberrances in synchronous (electrical) activity between different regions of the cortex, or loss of excitation-inhibition balance; e) On a computational level, these deficits are seen as aberrant encoding of the precision of prediction errors (usually ascribed to superficial pyramidal cells); and f) The prefrontal cortex, which is particularly implicated in psychosis, is still developing into early adulthood and therefore may show psychological vulnerability disclosed by neuromodulatory deficits at later stages of neurodevelopment.

However, one strand that is notably missing from this tapestry is immunology. As outlined above, the immune system plays a key role in the development of psychosis. This leaves open the questions, "Does this strand also have a place within the overarching picture of the dysconnection hypothesis? If so, how? If not, why not?" It is evident that prenatal development is a critical stage, in which environmental phenomena (and their interactions with genetic influences) have especially significant and enduring consequences for the neurodevelopment and mental health of the offspring (Brown & Meyer, 2018; Hall, Pain, et al., 2020; Langenhof & Komdeur, 2018; Van den Bergh et al., 2020). The question then is, "What is it about the immune response (as an environmentally-triggered phenomenon) that elicits or exacerbates wide-ranging psychopathology at this stage?" A reasonable, if general, explanation is

offered by the notion of 'allostatic load'. This term is broadly defined as "wear and tear" endured by an entire organism as a result of deviations from a homeostatic balance (McEwen, 1998). Allostasis literally means *homeostasis through change,* and refers to the process of adaption in the face of stress (or uncertainty, in computational terms (Peters et al., 2017)). This conceptual framework is highly applicable to both the immune system (which must maintain a delicate balance of response to threat) and the notions of risk and resilience, inasmuch as allostatic load tends to be higher in organisms that are unable to flexibly turn compensatory mechanisms on and off in accordance with the degree or presence of threat (McEwen, 1998; Peters et al., 2017). Indeed, the concept of allostatic load has recently been applied to explain the cumulative aetiology of psychosis – largely in terms of stress and endocrinology, but with some reference to the immune response (Misiak, 2019). The implication here is that it is possibly not infection, nor the immune response directly that elicit the pathophysiology of schizophrenia; but rather the allostatic load that is incurred because of them.

Aims

Friston et al. (2016) conclude by calling for studies that, "...close the explanatory gap between pathophysiology at the molecular (synaptic) level and the psychopathology experienced by patients," admitting that, "...we still need to identify the links between abnormal synaptic integration, polygenetic predisposition, epigenetics, region-specific gene expression and the implications for hierarchical inference in the brain." In light of this, the aims of this thesis are threefold:

1. To further 'close the explanatory gap' and attempt to bridge some of these disparate literatures by exploring the molecular mechanisms that underlie predictive coding and aberrant precision in psychosis.
2. To find a place for immunology within the framework of the dysconnection hypothesis and predictive coding.
3. To find a place for predictive coding in immunology to provide a complete account of allostasis as embodied inference – that rests upon both the brain and the immune system.

To this end, I call on three distinct, yet equally rich, bodies of psychosis research in this thesis: namely, theoretical neurobiology, cell biology and psychiatric genetics. *Chapter 1* is a transcriptome-wide association study of the MMN, exploring the genetic underpinnings of perceptual synthesis and synaptic gain control. *Chapter 2* presents a gene-environment interaction study showing how immune insults may interact with a genetic background associated with schizophrenia. Finally, *Chapter 3* generalises the notion of inference and applies it to the immune system. This generalisation can be summarised as embodied or immunoceptive inference – offering a first principles account of the immune response and its interactions with the brain.

Chapter 1

Transcriptome-wide association study reveals two genes that influence mismatch negativity

Abstract

The mismatch negativity (MMN) is a differential electrophysiological response measuring cortical adaptability to unpredictable stimuli. The MMN is consistently attenuated in patients with psychosis. However, the genetics of the MMN are uncharted, limiting the validation of the MMN as a psychosis endophenotype. I therefore perform a transcriptome-wide association study of 728 individuals, which reveals two genes (*FAM89A* and *ENGASE*) whose expression in cortical tissues is associated with the MMN. Enrichment analyses of neurodevelopmental expression signatures show that genes associated with the MMN tend to be overexpressed in frontal cortex during prenatal development but significantly downregulated in adulthood. Endophenotype Ranking Value calculations comparing the MMN and three other candidate psychosis endophenotypes (lateral ventricular volume and two auditory-verbal learning measures) find the MMN considerably superior. These results yield promising insights into sensory processing in the cortex and endorse the notion of the MMN as a psychosis endophenotype.

This chapter is adapted from Bhat, Irizar et al., *Cell Reports* (2021).

Introduction

Mismatch negativity as a measure of prediction error

The mismatch negativity (MMN) is an event-related potential that measures the cortical response to occasional "oddball" stimuli in an otherwise repetitive series (Näätänen, 1992; Naatanen et al., 1978). The MMN is interpreted as a "prediction error signal": the brain's response to sensory information that deviates from its prior "beliefs" (Friston, 2005; Garrido et al., 2009). This does not refer to propositional beliefs (participants in the MMN paradigm are instructed *not* to pay attention to stimuli presented); rather, an unconscious predictive processing that frames the brain as a statistical model of its environment which generates predictions about sensations, compares it to actual sensory input and updates itself to minimise discrepancies (Helmholtz, 1866/1962; Knill & Pouget, 2004). This updating depends upon the relative precision of prior beliefs and sensory evidence. Here, 'precision' is a measure of certainty and physiologically represents post-synaptic gain (excitability) of neurons reporting prediction errors (Parr & Friston, 2019). The lower the precision of sensory data (e.g., the more muffled a sound) or the higher the precision of prior beliefs (e.g., the more times the sound has been heard), the less readily these neurons fire action potentials – much as a scientist would ascribe reliability to experimental findings and weigh them against an existing body of literature (Parr & Friston, 2019). The MMN oddball paradigm is widely used because of its profundity, replicability and simplicity as a measure of how a brain adapts to a changing environment. The most common MMN paradigm involves presenting participants with 'standard' and 'deviant' tones (Erickson et al., 2016). The deviance can be in a variety of domains – including intensity, frequency or duration – as long as it departs from an established pattern (Kathmann et al., 1999). The MMN waveform is quantified as the difference between the event-related potentials elicited by the standard and deviant stimuli (Baldeweg & Hirsch, 2015).

MMN in psychosis

Psychosis is a highly heritable mental disorder characterised by hallucinations, delusions and cognitive deficits (American Psychiatric Association, 2013; Bergen et al., 2012; Brainstorm Consortium, 2018; Hilker et al., 2018; Johan H. Thygesen et al., 2020). It has recently been conceptualised as a disorder of aberrant precision: the precision-weighting of sensory stimuli are skewed (Limongi et al., 2018). This literature is very recent so the specific mechanisms of this aberrant precision are not well understood, but it has been suggested that prior beliefs may be 'overweighted' in hallucinations (Benrimoh et al., 2019; Powers et al., 2017) and 'underweighted' in the case of the MMN (R. A. Adams et al., 2013; Sterzer et al., 2018) relative to new sensory information. This is supported by the fact that patients with psychosis consistently show significantly smaller MMN than healthy controls (Erickson et al., 2016; Naatanen et al., 2012; Shelley et al., 1991). Moreover, the MMN is attenuated in patients *before* illness onset (Bramon et al., 2004; Hong et al., 2012) and is predictive of transition to psychosis in high-risk patients (Bodatsch et al., 2011; Erickson et al., 2016). The MMN also progresses with the disorder: first-episode psychosis patients show less attenuated MMN than chronic patients (Erickson et al., 2016; Haigh et al., 2017). The MMN is therefore considered a strong candidate endophenotype for psychosis.

MMN as an endophenotype of psychosis

Endophenotypes are biomarkers of structure or function that characterise an illness and indicate genetic liability (Bramon et al., 2005; Gottesman & Gould, 2003). Psychotic disorders such as schizophrenia and bipolar disorder with psychotic symptoms are heterogeneous and highly polygenic: more than 100 genetic loci have been associated with schizophrenia and over 30 with bipolar disorder with psychotic symptoms (Pardiñas et al., 2018; Psychosis Endophenotypes International Consortium et al., 2014; Stahl et al., 2019). The mechanisms by which these genetic variants affect the disease pathway remain unclear. Studying the genetics of a well-defined and objectively quantifiable endophenotype like the MMN has

strong potential to yield key insights into the biological mechanisms of psychosis development. However, an important criterion for a trait being a useful endophenotype is a substantial overlap in genetic architecture with the disease itself (Calafato & Bramon, 2019; Iacono et al., 2017). The likelihood of such an overlap has been indicated by research that shows attenuated mismatch in unaffected relatives of people with psychosis (Psychosis Endophenotypes International Consortium et al., 2014), but targeted genetic association methods have yet to be applied to the MMN to substantiate this phenomenon.

Transcriptome-wide association studies

Transcriptome-wide association studies (TWAS), like Genome-Wide Association Studies (GWAS), are a useful hypothesis-free method of studying how genetic variation influences a trait. Both GWAS and TWAS have been central to the study of psychosis, having identified 270 genetic loci and 175 genes reliably associated with schizophrenia, respectively (Gusev et al., 2018; Pardiñas et al., 2018; Psychosis Endophenotypes International Consortium et al., 2014; Ripke et al., 2020). While GWAS evaluate variation at the single nucleotide polymorphism (SNP) level, TWAS evaluate variation at a gene level (Gamazon et al., 2015; Gamazon et al., 2019; Gusev et al., 2018; Huckins et al., 2019). This is valuable for phenotypes like the MMN that are laborious to obtain and rarely collected in combination with genetic data, as the lower multiple-testing burden of gene-level associations allow TWAS to be well powered with much smaller sample sizes. Analysing gene expression also allows more direct inference of biological mechanisms: it is often difficult to deduce which biological pathways are implicated by GWAS-significant SNPs due to linkage disequilibrium and the poorly understood dynamics of non-coding regions of the genome (Gusev et al., 2018). The TWAS approach makes it possible to infer gene expression in a discovery dataset without having to collect tissue expression data. Specifically, TWAS evaluate the association between individual differences in genetically regulated gene expression and an outcome of interest. Expression levels are inferred based on a pre-existing reference dataset that contains

both genotype and tissue expression data (for example, Genotype-Tissue Expression (GTEx) Project database, which I use in the current study). For these reasons, I considered a TWAS to be the most appropriate method of exploring the genetics of the MMN.

The tissues I have selected from GTEx are the Brodmann Area 9 (BA9) region of the frontal cortex, as well as the whole cortex; chosen for their relevance to the phenotype. Previous functional magnetic resonance imaging (fMRI) studies have shown that the auditory MMN localises to the inferior frontal gyrus (IFG) and superior temporal gyrus (STG) (Doeller et al., 2003; Opitz et al., 2002). Although gene expression data are derived from post-mortem tissue samples which do not benefit from the task-based localisation afforded by neuroimaging methods such as fMRI, a broader level of localisation is sufficient for the purposes of this study as there is a very high likelihood of shared genetic signals between adjacent tissues (Ip et al., 2018). The two tissues overlap but I have chosen to analyse both for two reasons. Firstly, the STG is best accounted for by the 'whole cortex' tissue as tissue samples localised to the STG are not currently available in the GTEx database – or, to my knowledge, any other open-source databases. Secondly, there is a larger (and not entirely overlapping) set of genes available from GTEx for the whole cortex than for the frontal cortex.

Aims

Studying the genetic architecture of processes that underlie the MMN may elucidate biological and neurodevelopmental mechanisms that underlie sensory processing as well as psychosis. In this study, I aim to identify genes whose expression in cortical tissues are associated with the MMN, assess their relevance over the lifespan and evaluate the MMN as a psychosis endophenotype.

Methods

Collaboration statement

For this study, I used MMN and genetic data that were collected previously by other experimenters. I co-facilitated the formation of the consortium by which these datasets were combined along with my supervisors, Elvira Bramon and Aritz Irizar. PrediXcan models were developed by (Gamazon et al., 2015; Gamazon et al., 2019; Huckins et al., 2019; Wheeler et al., 2016) based on existing data from the Genome-Tissue Expression database (GTEx v7). I was responsible for the statistical analysis as well as write-up.

Participants

Participants were drawn from a consortium of three centres: University of Maryland (*n*=429), Harvard University (*n*=1736) and the London sub-sample of the Psychosis Endophenotypes International Consortium, *n*=5635 (Psychosis Endophenotypes International Consortium et al., 2014; Ranlund et al., 2016; Shaikh et al., 2012). All samples include patients with psychosis (schizophrenia or bipolar disorder with psychotic symptoms) and healthy controls. MMN data were acquired in a subset of each sample (see Supplementary Table 1). The London sample additionally contains unaffected relatives of patients with psychosis (*n* = 82). These relatives do not significantly differ in MMN from healthy controls in the same sample (*n* = 84; see results), so were treated as healthy controls for the purposes of this study. The collection of data used for this research was approved by the ethics committees at the participating institutions (including King's College London [References 011/99 and 038/00], the Metropolitan Multi-centre Research Ethics Committee [MREC/03/11/090] and University of Maryland). All participants gave written informed consent before they contributed to the study.

Measures

Clinical Assessments

To confirm a DSM-IV or V diagnosis, participants were assessed by a psychiatrist or trained researcher using the following scales: the Positive and Negative Syndrome Scale (Kay et al., 1987), the Schedule for Affective Disorders and Schizophrenia-Lifetime version, for the London and Harvard groups (Endicott & Spitzer, 1978) or the Structured Clinical Interview for DSM-V Axis 1 Disorders, for the Maryland group (First et al., 1997). Family history of any mental disorder was obtained using the Family Interview for Genetic Studies.

Procedure

MMN data collection

Electroencephalography data were collected using near-identical paradigms at the three centres where participants were recruited (Supplementary Table 1). Subjects were seated with their eyes open while wearing an electrode cap and presented, through earphones, with sequences of repetitive (standard) auditory stimuli, interspersed with occasional deviant stimuli. To ensure a *pre-attentive* event-related potential was being measured, the subjects were instructed not to pay attention to the sounds presented.

Auditory stimulus characteristics

The stimuli presented in the oddball paradigm were 73-80 dB, 1000 Hz tones, with a 0.3 second inter-stimulus interval (from offset to onset of consecutive stimuli). In the Maryland sample (n=429), 800 tones were presented in one block. In both the London (n=464) and Harvard (n=135) samples, 1200 tones were presented in three blocks of 400 tones. The standard stimuli were 60 (Maryland) or 25 (London and Harvard) milliseconds long with a 5ms rise/fall time. These comprised 80% (Maryland) or 85% (London

and Harvard) of tones presented. The deviant stimuli were 150ms (Maryland) or 50ms (Harvard and London) long with a 5ms rise/fall time.

EEG acquisition

Electroencephalography (EEG) data were collected using arrangements of 21-64 scalp sites (see Supplementary Table 1 for details of electrode arrangements in each sample) according to the 10/20 International System (all arrangements included the following primary electrodes: FP1, FP2, F7, F8, F3, F4, C3, C4, P3, P4, FZ, CZ, PZ, T3, T4, T5, T6). Recordings were grounded at FPZ using silver/silver-chloride electrodes (Klem et al., 1999) and referenced to the left ear lobe. Eye movements were monitored by vertical, horizontal, and radial electro-oculograms (EoGs). Data were continuously sampled at 1000 Hz (Maryland) or 500 Hz (London and Harvard) with a DC/100 Hz (Maryland) or 0.03 to 120 Hz (Harvard and London) band-pass filter (24 dB/octave roll-off). Impedances were kept below 6 kΩ.

EEG pre-processing

Data were re-referenced to common average and band-pass filtered 0.03 (London) or 0.1 (Harvard and Maryland) to 50 Hz. Ocular contamination from the data was removed using the artefact-aligned average procedure (London) (Croft & Barry, 2000) or regression-based weighting coefficients (Harvard and Maryland) (Semlitsch et al., 1986). Data were epoched from 100ms pre-stimulus to 300ms (London) or 400ms (Maryland and Harvard) post-stimulus. Epochs were averaged separately for the standard and deviant tones and then baseline corrected. The MMN was defined as the difference between the deviant and standard event-related potentials. Then the peak MMN (50 to 200ms post-stimulus for Harvard and London; 100 to 250ms post-stimulus for Maryland) was identified by a computer algorithm, which made the process blind to clinical group status. To ensure accurate peak detection, visual inspections of the

peaks detected by the algorithm were conducted blind to clinical group and other participant characteristics (Bramon et al., 2004; Hong et al., 2012). This approach (automated detection with blind visual checks) is optimal for large samples and prevents human error and biases.

Genotyping

DNA was obtained from blood for all participants. The Harvard DNA samples were extracted at the Massachusetts General Hospital Center for Human Genetic Research and genotyped at the Broad Institute using the Illumina OmniExpress Infinium Platform (Illumina Inc., San Diego, CA, USA). The London samples were genotyped with the Genome-wide Human SNP Array 6.0 at the Affymetrix Services Laboratory (www.affymetrix.com) and sent to the Wellcome Trust Sanger Institute (Cambridge, United Kingdom) for DNA quality control. The Maryland samples were genotyped on the Illumina Omni2.5-8 BeadChip.

Quality control of genotype data

London

Single nucleotide polymorphism (SNP) exclusion criteria for the entire London dataset were: study-wide missing data rate over 5% (11,610 SNPs excluded); having four or more Mendelian inheritance errors identified with PEDSTATS (Wigginton & Abecasis, 2005) (26,585 SNPS excluded); evidence for deviation from Hardy-Weinberg equilibrium ($p < 10^{-6}$; 2,404 SNPS excluded); minor allele frequency <0.02 (145,097 SNPs excluded); SNPs from X and Y chromosomes or mitochondrial DNA (38,895) and poor genotyping identified by visual inspection of intensity plots in Evoker (Morris et al., 2010) (9499 SNPs excluded). Sample exclusion criteria for London were: >2% missing SNP data (214 samples excluded); divergent genome-wide heterozygosity with inbreeding coefficients $F > 0.076$ or $F < -0.076$ seen in PLINK (Purcell et al., 2007) (70 samples excluded); chromosomal sharing (inferred from a genome-wide subset of 71,677 SNPs), where 70 duplicates and monozygotic twins were removed by

excluding one of each pair (whichever had less complete genotype data) of individuals showing identity by descent > 95%.

Harvard

As described in (Hall et al., 2015), quality control for the Harvard sample included the following steps: removing individuals with discordant sex information, missing genotype rate >5% or heterozygosity rate >3SD, shared IBD >0.125, or were non-European ancestry based on principal component analyses. Exclusion criteria for SNPs were as follows: SNPs on the X or Y chromosome, MAF<0.05, call rate <98%, and $P < 1 \times 10^{-6}$ for deviation from Hardy-Weinberg equilibrium. A total of 664,907 autosomal SNPs passed QC. Quality control steps were carried out with PLINK (Purcell et al., 2007).

Maryland

Single nucleotide polymorphism (SNP) exclusion criteria for the Maryland dataset were: study-wide missing data rate over 5; evidence for deviation from Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$) minor allele frequency <0.01; SNPs from X and Y chromosomes or mitochondrial DNA. Sample exclusion criteria for Maryland were: >5% missing SNP data (0 samples excluded); divergent genome-wide heterozygosity; identity by descent > 95%. A total of 1799738 autosomal SNPs passed QC. Supplementary Tables 4A-D show a full comparison of SNP and sample exclusion criteria across the three datasets.

Genotype imputation

Genotype imputation was performed separately on each dataset, using information from all individuals that passed genetic quality control (QC), regardless of whether MMN data had been acquired from them. Quality controlled genotypes were submitted to the Sanger Imputation Server (McCarthy et al., 2016; imputation.sanger.ac.uk), where the EAGLE2/PWBT (Durbin, 2014; Loh et al., 2016) pipeline was used for pre-phasing and imputation against the Haplotype Reference Consortium panel (r1.1). This yielded

~39.1 million imputed variants. The resulting genotypes were hard-called using a 0.8 genotype probability threshold and all variants with an INFO score < 0.8 were excluded. The original typed genotypes were then merged with the new imputed set such that, where the SNP positions were common to both, the typed data were given preference.

Quality control of imputed genotypes

QC was performed on imputed genotypes using PLINK. Imputed SNP exclusion criteria were: missing data rate of over 5%; minor allele frequency < 1%; departure from the Hardy-Weinberg equilibrium ($p < 1e^{-6}$); Mendelian error rate > 10%; and cases vs. controls data missingness significance < $5e^{-6}$. Sample exclusion criteria following imputation were: missing data rate of over 5%, Mendelian error rate > 5% and |inbreeding coefficient| > 0.1. LDAK (Speed et al., 2017) was used to identify duplicates or twins as pairs of individuals with a kinship coefficient > 0.95 (based on thinned set of SNPs) and remove one of each pair. After QC, 4835, 1602 and 411 individuals and ~6.5, ~7.3 and ~10.1 million SNPs were left for the London, Harvard and Maryland samples, respectively. Of these, EEG data were available for 254, 403 and 71 participants in the London, Maryland and Harvard samples, respectively. Supplementary Tables 5A-C show a full comparison of QC criteria for imputed data across each of the three datasets.

Statistical Analysis

Transcriptome-wide association study (TWAS)

I performed the TWAS using PrediXcan (Gamazon et al., 2015; Gamazon et al., 2019; Huckins et al., 2019; Wheeler et al., 2016). SNP-gene expression effect-weights were estimated by the PrediXcan developers using GTEx v7 data for brain cortex and frontal cortex from PredictDB (predictdb.org). Entering these expression weights (and the dosage matrices for the corresponding effect alleles) into PrediXcan, I imputed the genetic component of gene expression for 4329 and 3604 genes in the cortex

and frontal cortex, respectively. Note that the genes included in the GTEx data only partially overlap between tissues, so although one would expect there to be a high degree of inter-tissue signal sharing, this may not be visible in every instance. I then tested for association between the predicted expression of each gene in each tissue and the amplitude of the MMN at the Fz electrode. As PrediXcan does not allow for the addition of covariates, MMN amplitude values were pre-adjusted for clinical group, age, gender and lab where electroencephalographic data were collected. TWASs were run separately on each of the three data sets, London (n = 254), Harvard (n = 71) and Maryland (n = 403); and then combined them using a fixed-effect precision-weighted meta-analysis.

Gene-set enrichment analysis

Gene-set enrichment analyses (GSEA) were performed on the cortex and frontal cortex TWAS results for 134 nervous-system function gene-sets (Hall, Medway, et al., 2020; Pardiñas et al., 2018; Pocklington et al., 2015) from the Mouse Genome Informatics database (Blake et al., 2014). The information required from this database is, broadly, lists of genes that are known to interact with each other as a part of a 'pathway' that performs a particular biological function, in order to assess whether these groups of genes together show significant associations with the phenotype (MMN) in the current sample. It is easier to conduct experiments investigating the functions of gene pathways on mice, which makes this database a rich resource. Furthermore, many such pathways are well conserved through mammalian evolution, so the Mouse Genome Database is commonly used (Bentley et al., 2019; Grama et al., 2020; Hall, Medway, et al., 2020; Lim & Kim, 2019) as a source for pathway-based analyses with human samples. Previous human ortholog genome-wide and transcriptome-wide association studies (Grama et al., 2020; Hall, Medway, et al., 2020) have indeed shown enrichment of gene sets from the Mouse Genome Database.

Linear mixed-effects regression-based competitive GSEA was implemented as previously described (Pain et al., 2019), using TWAS-GSEA (github.com/opain/TWAS-GSEA). The lme4qtl R

package (Ziyatdinov et al., 2018) was used for mixed model regressions, where the -$\log_{10}$ *p*-values from the TWAS were used as dependent variables. The gene set membership of each gene was included as a fixed effect predictor and the matrix of correlations between predicted expression of each gene was included as a random effect. The gene correlation matrix was added to the regressions to account for linkage disequilibrium.

Neurodevelopmental signature enrichment

To look for enrichment in the MMN TWAS results of highly expressed or suppressed genes across neurodevelopmental stages, expression data for the two tissues of interest were downloaded from the BrainSpan Atlas project (www.brainspan.org). The dataset contains RNAseq data (Reads Per Kilobase of transcript, per Million: RPKMs) for 524 brain tissue samples from 42 individuals (19 females/23 males) aged eight weeks post-conception to 40 years old. RPKM values were $\log_2$-transformed and lowly expressed genes ($\log_2$ RPKM < 2^{-7} in 90% or more of the samples; 17389 genes) were subsequently removed. Samples were grouped into nine age-ranges and brain tissue samples were grouped into nine brain regions (Supplementary tables 6A and B). To generate gene expression signatures for each age group (versus the other age groups), I ran linear regressions (Equation 1).

$$\mathrm{GEx} \sim \beta 0 \; + \; \beta 1 \cdot \mathrm{AgeGr} \; + \; \beta 2 \cdot \mathrm{AgeGr{:}\,CortexRg} \; + \; \beta 3 \cdot \mathrm{BrainRg} \; + \; \beta 4 \cdot \mathrm{Gender} \; + \; \varepsilon$$

Equation 1. GEx = gene expression; **AgeGr** = dummy variable for age-group of interest; **CortexRg** = dummy variable for region of interest (whole cortex/frontal cortex); **BrainRg** = variable containing 9 broad brain regions.

Correlation between samples from the same individuals was accounted for by incorporating the intra-donor correlation into the covariance matrix when evaluating regressions. The final age-group expression signatures were generated by fitting a contrast with the sum of the coefficients of the age-group ($\beta 1$) and

of the interaction between age-group and brain region of interest ($\beta 2$). The differential expression analysis was performed with the R package 'limma' (Ritchie et al., 2015). Enrichment for these neurodevelopmental expression signatures in the TWAS results was tested using linear mixed models, using lme4qtl (Ziyatdinov et al., 2018). The logarithm of the *p*-value of each gene in the TWAS ($-\log_{10}$ *p*-value) was used as the dependent variable, the signed logarithm of the *p*-values of the corresponding neurodevelopmental signature (sign (*effect size*) × $-\log_{10}$ *p*-value) as the fixed effect predictor and the matrix of correlations between genes as a random effect.

Endophenotype Ranking of the MMN

The ERV is an index created to objectively quantify the genetic utility of an endophenotype. It varies from 0-1; higher values indicate that the endophenotype and the illness are more strongly influenced by shared genetic factors (Glahn et al., 2012). Endophenotype Ranking Value (ERV) for MMN (specifically, SNP-based ERV, or ERV_{SNP}) was calculated using the bivariate Genome-Based Restricted Maximum Likelihood (GREML) function (Lee et al., 2012; Yang et al., 2010) in the Genome-wide Complex Trait Analysis (GCTA) tool (Yang et al., 2011) to estimate the SNP-based heritability of MMN (h_e^2) in the largest dataset (Maryland; n = 403). Age and gender were included as covariates in this estimation. For schizophrenia (h_i^2), the heritability estimate (0.2002) was extracted based on a population prevalence of 0.4% (Pardiñas et al., 2018). These two heritability estimates and the genetic correlation (ρ_g) between MMN and schizophrenia were used to calculate the ERV according to the following equation:

$$ERV_{ie} = |\sqrt{h_i}^2 \sqrt{h_e}^2 \rho_g|$$

Results

Demographics

After all quality control procedures, a total of 728 participants (302 with psychosis and 426 healthy controls) with both genetic and MMN data were available for analysis (unaffected relatives from the London sample were treated as healthy controls in the current study; see Methods). There was no significant difference in age between control (M = 40.25 years; SD = 15.28 years) and patient (M = 38.70 years; SD = 12.92 years) groups across the whole sample (n = 728, t = 1.431, p-value = 0.153). There was a significantly smaller proportion of female participants amongst patients (31.79%) compared to controls (58.45%) across the whole sample (n = 728, χ^2 = 49.325, p-value = $2.169e^{-12}$). A description of the sample can be seen in Table 1.

Table 1. Demographics and clinical characteristics of the sample after genetic quality control[c]

	Maryland			**Harvard**			**London**			
	Patient	**Control**	**Overall**	**Patient**	**Control**	**Overall**	**Patient**	**Relative**	**Control**	**Overall**
N	164	239	403	54	17	71	84	82	88	254
% Females	28	56.5	44.9	38.9	58.8	43.7	34.5	59.8	62.6	52.4
Age[a,b]	36.1 ± 13.5	38.7 ± 16.1	37.6 ±15.1	43.8 ± 11.3	36.9 ± 15.9	42.1 ±12.8	40.5 ± 11.7	46.7 ± 13.8	39.2 ± 12.5	42.0 ± 13.0
Age range[b]	11-63	9-80	9-80	21-66	21-63	21-66	18-65	17-73	18-62	17-73

[a] In years

[b] Mean ± Standard deviation

MMN amplitude is attenuated in patients with psychosis

Table 2 shows the average MMN (with standard deviation) for each dataset included in this study, as well as for patients, relatives (for PEIC) and controls within each dataset. Please see Supplementary Figures 1 and 2 for MMN waveform plots for the Maryland (n = 403) and Harvard (n = 71) samples. MMN plots from the London sample (n = 254) have been published previously in (Bramon et al., 2004) and (Ranlund et al., 2016).

Table 2. Mean mismatch negativity amplitude[b] at FZ (μV) in each of the datasets by group

Sample	Patients	Controls	Relatives	Whole dataset	% Decrease[c]
Maryland[a]	-1.09 ± 1.43	-1.59 ± 1.78	-	-1.39 ± 1.66	31.7%
Harvard[a]	-1.10 ± 2.20	-2.18 ± 2.27	-	-1.36 ± 2.25	49.4%
PEIC[a]	-2.52 ± 1.24	-3.15 ± 1.59	-3.27 ± 1.56	-2.98 ± 1.5	20.1%

[a]Mean ± Standard deviation (in μV)

[b]These values are unadjusted for covariates

[c]Percent reduction in patients compared to unaffected subjects (average of relatives and controls, for PEIC)

Age-, gender- and lab-adjusted linear regressions revealed a significantly attenuated MMN Fz peak amplitude in psychosis patients in the whole sample (n = 728, effect size = 0.70μV, *95% CI* = 0.45μV to 0.94μV, p = $3.5e^{-8}$) as well as in each of the two largest datasets (Maryland: n = 403, *coef* = 0.48μV, *95% CI* = 0.14μV to 0.82μV, p = $6e^{-3}$; London: n = 254, *coef* = 0.66μV; *95% CI* = 0.23μV to 1.11μV, p = $3e^{-3}$). There was no difference of the MMN in psychosis patients in the smallest sample (Harvard; n = 71, coef = -0.01μV; *95% CI* = -1.59μV to 1.57μV, p = 0.99), most likely due to limited statistical power of this sample (a sample of 71 is too small to yield meaningful genetic association results on its own). However, in the combined sample of 728 participants, the group comparisons are consistent with the literature, with significantly reduced MMN in patients with psychosis (Supplementary Table 3).

Within the London sample, a linear regression which included age, gender and testing laboratory as covariates, showed no significant difference in MMN amplitude at the Fz electrode between unaffected relatives of patients with psychosis and healthy controls – indeed, unaffected relatives appeared to have slightly (insignificantly) enhanced MMN compared to controls (effect size = -0.297, SE = 0.234, p-value = 0.205, 95%CI = -0.76 to 0.16).

To assess the effect of stimulus duration on the MMN, the cohorts that used shorter stimuli (London and Harvard) were compared with the cohort that used longer auditory stimuli (Maryland) in their MMN paradigm, by linear regression with age, gender and clinical group as covariates. In the Maryland group (n = 403, M = -1.39 μV, SD = 1.66 μV), MMN was smaller than the shorter stimuli groups (n = 325, M = -2.63 μV, SD = 1.82 μV). The model explained 17.47% of the variance, and was a significant predictor of MMN amplitude, $F(5,722) = 30.56$, $p < 2.2 \times 10^{-16}$; stimulus length contributed significantly to this difference (*effect size* = -1.16μV, $p = 2.63 \times 10^{-16}$). The latency of MMN at FZ in the Maryland group (M = 186.6ms, SD = 29.63ms) was later than the shorter stimuli groups (n = 166, M = 132.19, SD = 45.95); stimulus length contributed significantly to this difference (*effect size* = -44.35, $p < 2 \times 10^{-16}$).

Increased *FAM89A* and *ENGASE* expression is associated with attenuated MMN

In the transcriptome-wide association study (TWAS) of MMN peak amplitude, at the Benjamini-Hochberg-corrected significance threshold (*FDR* = 0.05), there are two genes that were significantly positively associated with MMN (Figure 1): *ENGASE* in whole cortex (effect size = 1.09; *p*-value = 1.06e-05; *FDR* = 0.045; *95% CI* = 0.60 to 1.58) and *FAM89A* in the frontal cortex (effect size = 0.82; *p*-value = 1.1e-05; *FDR* = 0.045; *95% CI* = 0.46 to 1.19). Multiple test correction was performed to account for all genes tested across both tissues. A heatmap showing the strength and direction of association for the top 10 genes in the TWAS can be found in Figure 2A. For the entire table of TWAS results from all

genes included in the analysis, please see Supplementary Table 2. The MMN peak is the *negative* component of the waveform obtained by subtracting the response to the standard stimulus from the response to the deviant stimulus. This means here that higher expression of *FAM89A* or *ENGASE* results in attenuated MMN amplitudes. For the frontal cortex, there were 26 SNPs in the PrediXcan gene model for *FAM89A* (R^2 (i.e., prediction accuracy) = 0.2798; p = 2.01 x 10^{-8}). For the whole cortex, there were 40 SNPs in the PrediXcan model for *FAM89A* (R^2 = 0.3471; p = 1.86 x 10^{-12}) and 23 SNPs in the gene model for *ENGASE* (R^2 = 0.0361; p = 0.0426).

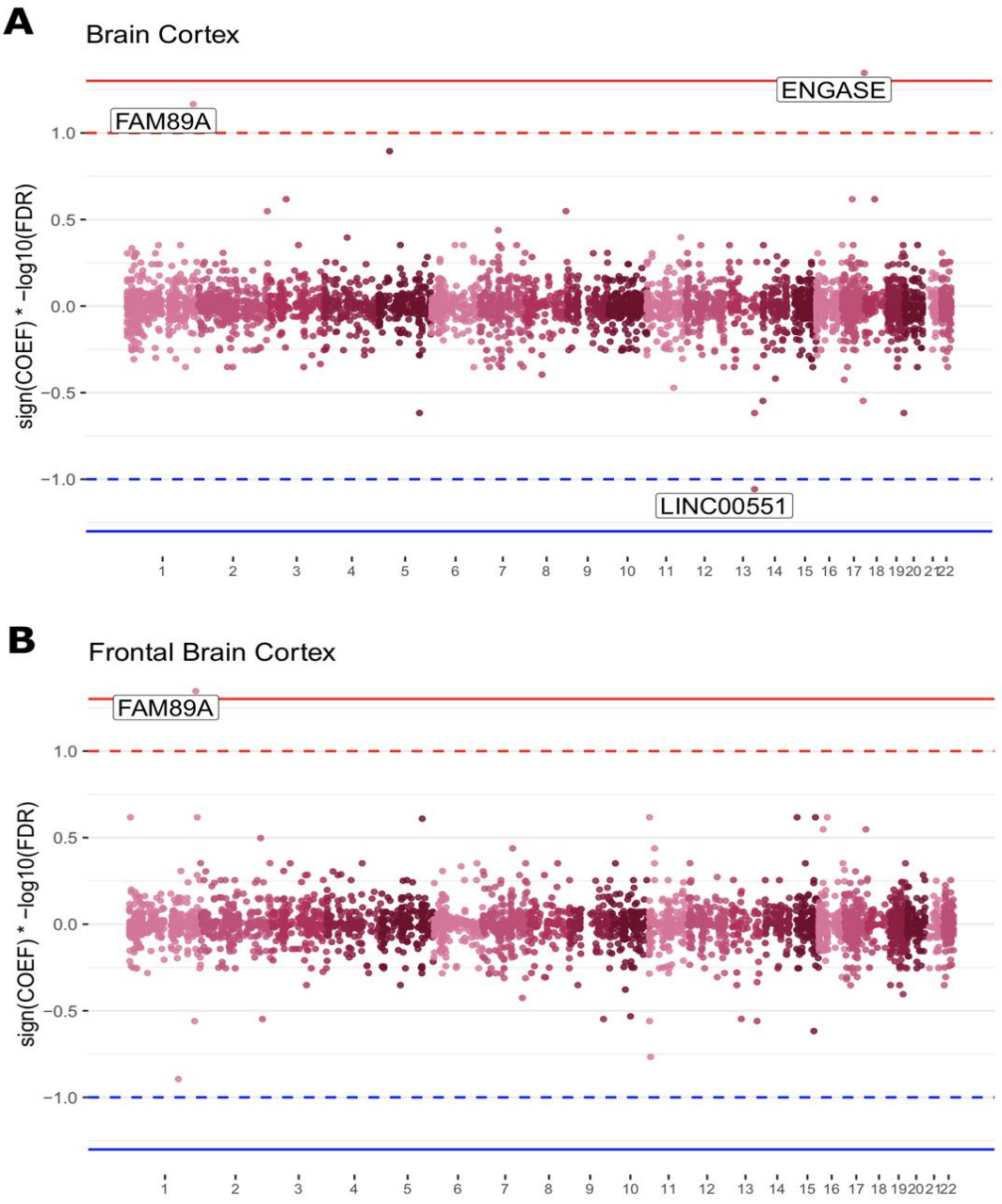


Figure 1. Transcriptome-wide association of 4329 and 3604 genes in the cortex and frontal cortex, respectively, shows *FAM89A* and *ENGASE* to be significantly associated with MMN. The Manhattan plots show, by tissue, the significance (-$\log_{10}$ *FDR*) of all genes in the TWAS of MMN, multiplied by the sign of the coefficient to show the direction of the effect [(sign(coefficient)]. **A.** Predicted expression of *ENGASE* in the whole cortex is significantly positively associated with MMN peak amplitude at the *FDR*<0.05 threshold indicated by the solid line. Genes within the dotted line show a (non-significant) association with MMN within a threshold of *FDR*<0.1. **B.** Predicted expression of *FAM89A* in the frontal cortex is significantly (*FDR*<0.05) positively associated with MMN peak amplitude.

Genes controlling neurotransmitter levels are enriched in MMN associations

In the MMN-TWAS results for the frontal cortex, one gene set ("Abnormal Neurotransmitter Level") is significantly enriched (over-represented) at the *FDR*<0.05 threshold (Table 3). There were no significantly enriched gene sets in the whole cortex.

Table 3. One gene set enriched for MMN at *FDR* < 0.05 and two (non-significant) at *FDR* < 0.1

Gene set	Genes in set	Genes tested	Beta	SE[a]	t-stat	*p*-value	FDR[b]
Abnormal neurotransmitter level	69	11	0.6579	0.187	3.5213	2.15×10^{-4}	0.045
Abnormal parental behaviour	204	20	0.4624	0.140	3.3027	4.79×10^{-4}	0.050
Abnormal behavioural response to xenobiotic	79	12	0.2945	0.097	3.0354	1.20×10^{-3}	0.084

[a] Standard Error (beta)
[b] False Discovery Rate

Genes that influence the MMN are under-expressed in adulthood

In the neurodevelopmental signature enrichment analysis, genes more strongly associated to MMN in the TWAS for frontal cortex are significantly under-expressed in the adult age categories of eighteen to twenty-three years (effect size = -0.0086; *p*-value = 0.0473; *SE* = 0.0043) and thirty to forty years (effect size = -0.0074; *p*-value = 0.0185; *SE* = 0.0032). Although not significant, the prenatal stages show a relative upregulation of higher *p*-value TWAS genes (Figure 2B). A rank-based identification of the top ten genes driving the association between the TWAS results and gene expression within the earliest (eight to twelve weeks post-conception) and latest (and thirty to forty years) categories (Figures 2C and 2D, respectively) reveals four genes (*BARD1, RBAK, SLAIN2* and *DOCK7* – all ranked within the top thirty genes in the MMN TWAS results) that are strongly overexpressed in the early prenatal stage and strongly downregulated in adulthood. The top ten genes driving this result also individually show a marked

overexpression in the earliest prenatal stage and a gradual decrease in expression over neurodevelopment, although *ENGASE* and *FAM89A* do not follow this pattern (Figure 2E). The significant downregulation in adulthood was not seen in the whole cortex, but nominal prenatal overexpression can also be observed here (see Supplementary Figure 3).

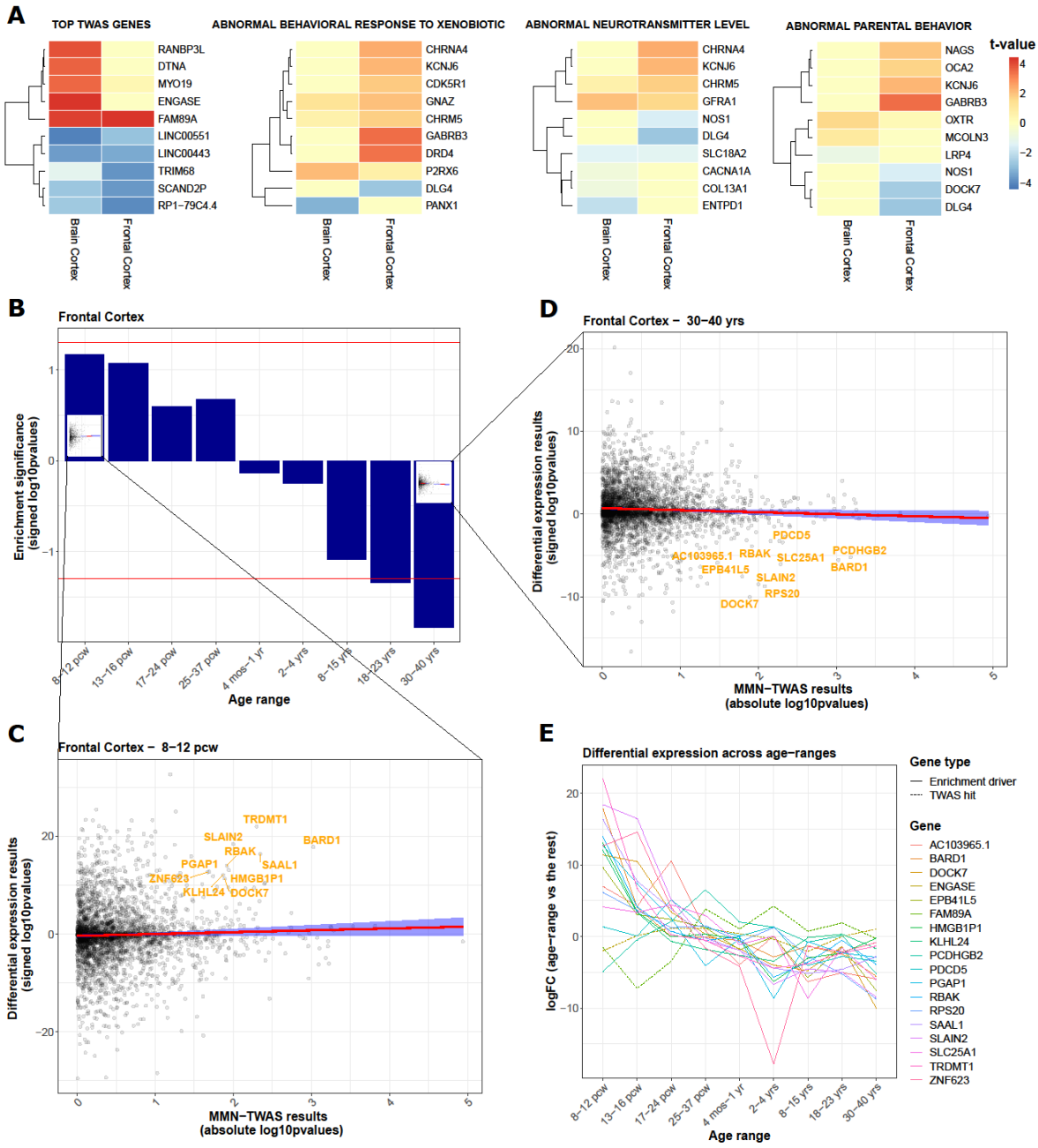


Figure 2. Gene set and neurodevelopmental stage enrichment analyses of MMN TWAS results show enrichment of genes controlling neurotransmitter level and downregulation of MMN-associated genes in adulthood. A. The first heatmap shows association strengths (*t*-statistics) and directions of association (red = positive; blue = negative) of the ten top MMN TWAS genes. The other heatmaps correspond to each of the three gene sets enriched for MMN and the constituent genes primarily driving these gene set-MMN associations. **B.** Expression of MMN-related genes across neurodevelopmental stages. Each bar of the bar plot represents an age range and the *p*-value of an underlying association analysis which assessed whether the genes more strongly associated to MMN in the TWAS were significantly up- or down-regulated in the frontal cortex within that age range. The last 2 bars reach the threshold of $p<0.05$, showing a significant downregulation of MMN-related genes in older age-groups. **C.** The regression analysis represented by the first bar of the bar plot, which tests the association between (absolute value of) *p*-values of genes examined in the MMN TWAS and the (signed -$\log_{10}$) *p*-values of genes assessed in a differential expression analysis between each age range and all the others. The slope shows a slight positive relationship between MMN-related genes and the gene expression profile of the 8-12-week post-conception neurodevelopmental stage. **D.** The regression analysis represented by the last bar of the bar plot, showing a negative relationship between MMN-related genes from the TWAS and the gene expression profile of the 30-40 years neurodevelopmental stage. **E.** Differential expression across the nine age-range categories of the 16 genes most responsible for driving the trend in downregulation of MMN-related genes.

MMN ranks higher than verbal recall and ventricular volume as a psychosis endophenotype

In order to estimate the utility of the MMN to understand more about the genetics of psychosis, the SNP-based ERV (ERV_{SNP}, a 0-1 scale value representing genetic overlap between phenotype and illness (Glahn et al., 2012)) of the MMN was calculated – in addition to that of three comparator phenotypes that have previously been associated with psychosis risk (Johan H. Thygesen et al., 2020). The results (Figure 3) show that the ERV_{SNP} for the MMN (0.28) is substantially higher (there is no overlap between the lower bound of the confidence area and the upper bounds thereof for the other endophenotypes) than those of lateral ventricular volume (0.02), RAVLT-delayed (0.10) and RAVLT-immediate (0.13). ERV is a standardized covariance so does not have units; it is calculated based on heritability and genetic correlation estimates for each phenotype. These estimates have wide confidence intervals in this analysis (Supplementary Table 7), so must be interpreted cautiously.

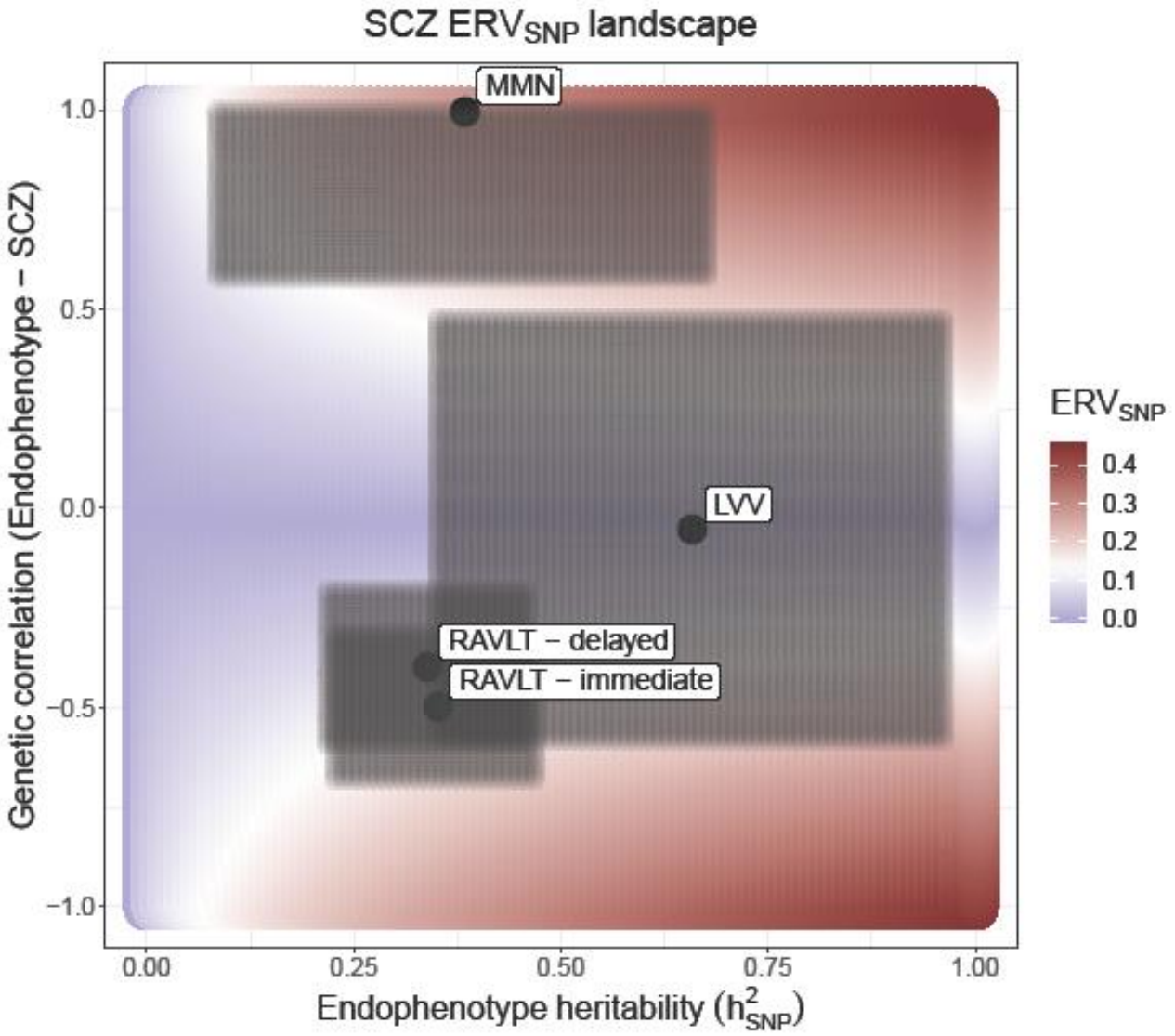


Figure 3. MMN ranks higher than working memory and ventricular volume in comparison of Endophenotype Ranking Values (ERV_{SNP}) of schizophrenia candidate endophenotypes. The graph shows a comparison of SNP-based Endophenotype Ranking Values (ERV_{SNP}) of MMN compared to ERV_{SNP}s of Ray Auditory Verbal Learning Task (RAVLT) immediate recall, RAVLT delayed recall and brain lateral ventricular volume (LVV). The colour scale indicates the ERV strength: a good endophenotype would sit in darker red or darker blue areas, indicating that it has a high degree of pleiotropy with the disease and is strongly heritable itself. ERV here has a maximum value of 0.447, given a SNP-based heritability (h^2_{SNP}) for schizophrenia of 0.2002 (Pardiñas et al, 2018). The shaded confidence areas in grey indicate the standard errors of the endophenotype heritability estimates (h^2_{SNP}) along the *x*-axis and of the genetic overlap between the endophenotype and schizophrenia along the *y*-axis. The ERV is a standardized genetic covariance and does not have units.

Discussion

The transcriptome-wide association study (TWAS) of mismatch negativity (MMN) revealed two genes whose expression is significantly positively associated with MMN: *FAM89A* (frontal cortex) and *ENGASE* (whole cortex). This means that increased expression of these genes relates to attenuated MMN amplitudes. Both genes are protein-coding, but relatively little is known about their functions. *FAM89A* (Family with Sequence Similarity 89 Member A) encodes a protein that contributes to cytoskeletal organization, modulation of protein synthesis and neurite outgrowth (Gurol et al., 2015). It is highly expressed in placental tissue, and interacts with the biogenetic protein *UBX2NB*, which is highly expressed in the foetal brain (www.string-db.org), suggesting a role for *FAM89A* in prenatal neurodevelopment. Functionally, *FAM89A* appears to be primarily involved in the immune response: it differentiates between viral and bacterial infections (Gomez-Carballa et al., 2019), is implicated in glial tumours (Pan et al., 2019), and is downregulated on exposure to interleukins 10 and 13 (Alevy et al., 2012; Trandem et al., 2011).

ENGASE (Endo-beta-N-acetylglucosaminidase) acts as a cytosolic enzyme that breaks down oligosaccharides and is involved in degradation of asparagine-linked N-glycans (Shi & Trimmer, 1999; Suzuki et al., 2002). Asparagine-linked N-glycosylation patterns influence the unique functional properties of potassium channels in the mammalian brain (Shi & Trimmer, 1999). The signalling of sensory precision is thought to be physiologically synonymous with neuromodulatory gain control (Moran et al., 2013), in which potassium channels play a central role (Delmas & Brown, 2005). It is possible that increased expression of *ENGASE* results in excessive degradation of asparagine-linked N-glycans, thereby altering the functional properties of synaptic potassium channels. If so, this would inevitably affect neuromodulation, which would be consistent with the loss of gain control of pyramidal cells computationally associated with aberrant sensory precision and reduced MMN (R. A. Adams et al., 2013). Deletions of *ENGASE* have been shown (in mice) to be protective against the embryonic lethality

of deletions *NGLY1*, which codes for N-glycanase-1, another deglycosylating enzyme (Fujihira et al., 2017).

The gene set significantly associated with MMN in this analysis was 'Abnormal Neurotransmitter Level', indicating that the genes whose expression influences predictive processing in the brain could also be involved in regulating the concentration of neurotransmitters in synaptic clefts. One of the most significantly associated genes within this gene set (shown in the third heatmap in Figure 2) is *KCNJ6*, which encodes the GIRK2 protein, an inward rectifier potassium channel which is ubiquitous in the brain and functionally present in glutamatergic synapses (Saenz del Burgo et al., 2008). The most significant (negatively) associated gene in this gene set was *DLG4*, which encodes PSD95 (Postsynaptic Density Protein 95): another well-studied protein that regulates synapses by trafficking (glutamatergic) NMDA and AMPA receptors (Coley & Gao, 2018). PSD95 is also implicated in schizophrenia and autism (Coley & Gao, 2018). These associations reinforce the notion that MMN and psychosis share a genetic component.

The genes that have more influence over MMN were, overall, under-expressed in adulthood. This could be interpreted to mean that genes that influence MMN (i.e., the genes likely to be involved in establishing neuronal structures that optimise the short-term plasticity necessary for belief updating) are also involved in early neurodevelopment. This would make sense, as there is a higher likelihood of encountering novel stimuli earlier in life (Koster et al., 2020). The specificity of the neurodevelopmental enrichment results to the frontal cortex is consistent with source localisation of MMN in previous studies (Dima et al., 2012; Ranlund et al., 2016).

The Endophenotype Ranking Value (ERV) analysis endorses the notion of MMN being an endophenotype of psychosis. The ERV of MMN (0.28) was substantially greater than those obtained for the other three candidate endophenotypes (0.02 – 0.13), considering the maximum possible value in this analysis was 0.447. However, due to the small sample size, the standard errors of the heritability and

genetic correlation estimates were large, so this result would require independent replication in a larger sample. ERV is a recent development in the field, so there is limited precedent upon which to specify a minimum sample size for meaningful results. For context, the original paper which proposed ERV as a formal approach to the identification of endophenotypes (Glahn et al., 2012) used a sample size of 1222 individuals to calculate family-based heritability of endophenotypes and their genetic correlation with disease liability. There are three factors I consider to be of importance here: the heritability of the endophenotype, the heritability of the disease and the novelty of the findings. The first two are important as the ERV is directly derived from these measures; in this sense, a good sample size for ERV is a good sample size for calculating heritability estimates. Stanton-Geddes et al. (2013) suggest that, with samples drawn from relatively well-controlled environments, sample sizes of a few hundred can yield meaningful SNP-based heritability estimates). Importantly, it has not been possible before to formally assess the utility of MMN as an endophenotype for psychosis, although it is one of the most likely candidates thereof. The ERV presented here for MMN therefore presents a principled starting point for gauging the value of MMN as a psychosis endophenotype.

There are some limitations to the current study. Firstly, as genetic association studies benefit from large samples, independent replication of this research in another large sample would be important. Secondly, in order to assemble a large enough dataset for a genetic association study, I combined samples that used slightly different MMN paradigms. These minor differences in methodology were accounted for by combining the samples by meta-analysis, as well as by including testing centre as a covariate in the regression analyses. However, future studies would ideally use a homogenously tested sample.

In summary, this study lays important groundwork for developing a clearer picture of the neurobiological mechanisms that result in the phenomenon of mismatch negativity and its attenuation in psychosis. The findings herein support the use of MMN as an endophenotype for psychosis and implicate *FAM89A* and *ENGASE* as key components of the physiology of prediction error minimisation.

Supplementary Information

Supplementary Table 1. Comparison of the sample sizes, data collection and processing procedures used in the three samples

	PEIC	**Harvard**	**Maryland**
Demographics			
Subjects with MMN data	**464**	**135**	**429**
Subjects with MMN and genetic data	**254**	**71**	**403**
% Patients in the sample diagnosed with schizophrenia	**61**	**77**	**100**
% Patients diagnosed with type 1 bipolar disorder with psychosis	**39**	**19**	**0**
% Patients with other psychotic disorders	**0**	**4**	**0**
MMN Paradigm			
Subject position/ instructions	Seated, eyes open/disregard all sounds presented	Seated, eyes open/disregard all sounds presented	Seated, eyes open/disregard all sounds presented
Auditory stimulus amplitude (decibels)	80	80	73 (measured at headphone coupler)
Auditory stimulus frequency (Hz)	1000	1000	1000
Inter-stimulus interval (s)	0.3	0.3	0.3
Total number of stimuli	1200	1200	800
Number of stimuli per block	400	400	800

Number of blocks	3	3	1
Standard stimuli			
Duration (ms)	25	25	60
Rise/fall time (ms)	5	5	5
Percentage of stimuli presented	85	85	80
Deviant stimuli			
Duration	50	50	150
Rise/fall time	5	5	5
Percentage of stimuli presented	15	15	20
EEG Acquisition			
Number of scalp sites	21/40/64 (3 systems)	21	64
Ground position	FPZ	FPZ	Midway between FPZ and FZ
Electrodes	Silver/silver chloride	Silver/silver chloride	Silver/silver chloride
Reference	Left earlobe	Left earlobe	Nose
Electro-oculogram	Vertical, horizontal, radial	Vertical, horizontal, radial	Vertical, horizontal
Acquisition Software	Neuroscan Stim	Neuroscan Stim	Neuroscan Stim
Amplifier	Nihon Kohden PV-441A (21 channels), NeuroscanNuAmps (40 channels), NeuroscanSynamps (64 channels).	Neuroscan Synamps	Neuroscan Synamps2 and Synamps2 RT
Continuous sampling frequency (Hz)	500	500	1000
Impedance (kΩ)	<5	<5	<5

Octave Roll-Off/Db	24	24	24
Acquisition parameters			
High-pass filter (Hz)	0.03	0.03	Direct current
Low-pass filter (Hz)	120	120	100
EEG Pre-processing			
Ocular artefact removal	Artefact-aligned average (Croft & Barry, 2000) or Regression-based weighting coefficients (Semlitsch et al, 1986)	Regression-based weighting coefficients (Semlitsch *et al*, 1986)	Regression-based weighting coefficients
Re-referencing	Common average	Common average	n/a
Offline band-pass filter (Hz)			
High-pass	0.03	0.1	0.1
Low-pass	50	20	30
Epochs			
Pre-stimulus (ms)	(-)100	(-)100	(-) 100
Post-stimulus (ms)	300	400	400
Averaging of standard & deviant tones	Separately, then baseline corrected	Separately, then baseline corrected	Separately
MMN Measurement			
Peak identification	Algorithm (blind to all clinical parameters)	Algorithm (blind to all clinical parameters)	Algorithm (blind to all clinical parameters)
Measurement window (ms)	50 to 200	50 to 200	100 to 250
Genetic Data			
Genotyping Chip	Affymetrix Genome-wide Human SNP Array 6.0	Illumina OmniExpress Infinium Platform	Illumina Omni2.5-8 BeadChip

Imputation server	Sanger Imputation Server (McCarthy et al., 2016; https://imputation.sanger.ac.uk/)	Sanger Imputation Server (McCarthy et al., 2016; https://imputation.sanger.ac.uk/)	Sanger Imputation Server (McCarthy et al., 2016; https://imputation.sanger.ac.uk/)
Pre-phasing	The EAGLE2 (Loh *et al*., 2016)	The EAGLE2 (Loh *et al*., 2016)	The EAGLE2 (Loh *et al*., 2016)
Imputation	PBWT (Durbin, Bioinformatics, 2014)	PBWT (Durbin, Bioinformatics, 2014)	PBWT (Durbin, Bioinformatics, 2014)
Imputation Reference Panel	Haplotype Reference Consortium panel (r1.1)	Haplotype Reference Consortium panel (r1.1)	Haplotype Reference Consortium panel (r1.1)

Supplementary Table 2. TWAS results for all genes with $FDR_T < 0.05$

Gene ID	Chr	Gene	Gene type	Status	Beta	T stats	P value	S.E.[1]	Tissue	FDR_T[2]	FDR_O[3]
ENSG000	chr17	ENGASE	Protein coding	KNOWN	1.08973	4.4037	#######	0.24745	Cortex	0.04567	0.04503
ENSG000	chr1	FAM89A	Protein coding	KNOWN	0.82464	4.3870	#######	0.18797	Frontal Cortex	0.04075	0.04503
ENSG000	chr1	FAM89A	Protein coding	KNOWN	0.68683	4.2051	#######	0.16333	Cortex	0.05598	0.06817
ENSG000	chr13	LINC00551	lincRNA	NOVEL	-	-	#######	0.15696	Cortex	0.06391	0.08755
ENSG000	chr1	RP1-79C4.4	lincRNA	NOVEL	-	-	#######	0.07174	Frontal Cortex	0.15251	0.12743
ENSG000	chr5	RANBP3L	Protein coding	KNOWN	0.49753	3.8966	#######	0.12768	Cortex	0.10464	0.12743
ENSG000	chr11	TRIM68	Protein coding	KNOWN	-	-	0.00015	0.24123	Frontal Cortex	0.18087	0.17129
ENSG000	chr18	DTNA	Protein coding	KNOWN	1.22744	3.6544	0.00025	0.33587	Cortex	0.22121	0.24140
ENSG000	chr15	SCAND2P	pseudogene	KNOWN	-	-	0.00029	0.22823	Frontal Cortex	0.21225	0.24140
ENSG000	chr17	MYO19	Protein coding	KNOWN	0.46698	3.5559	0.00037	0.13132	Cortex	0.24112	0.24140
ENSG000	chr13	LINC00443	lincRNA	KNOWN	-	-	0.00039	0.14308	Cortex	0.24112	0.24140
ENSG000	chr5	PCDHB3	Protein coding	KNOWN	-	-	0.00046	0.13190	Cortex	0.24844	0.24140
ENSG000	chr15	ZNF710	Protein coding	KNOWN	0.62431	3.4718	0.00051	0.17981	Frontal Cortex	0.21225	0.24140
ENSG000	chr19	ZNF580	Protein coding	KNOWN	-	-	0.00053	0.20523	Cortex	0.24941	0.24140
ENSG000	chr15	GABRB3	Protein coding	KNOWN	2.00640	3.4528	0.00055	0.58108	Frontal Cortex	0.21225	0.24140
ENSG000	chr1	WRAP73	Protein coding	KNOWN	0.44390	3.4467	0.00056	0.12878	Frontal Cortex	0.21225	0.24140
ENSG000	chr3	ATXN7	Protein coding	KNOWN	1.30513	3.4402	0.00058	0.37936	Cortex	0.24941	0.24140
ENSG000	chr16	SEZ6L2	Protein coding	KNOWN	0.70893	3.4327	0.00059	0.20652	Frontal Cortex	0.21225	0.24140
ENSG000	chr11	DRD4	Protein coding	KNOWN	0.75060	3.4265	0.00061	0.21905	Frontal Cortex	0.21225	0.24140
ENSG000	chr1	ERO1LB	Protein coding	KNOWN	0.55797	3.4245	0.00061	0.16293	Frontal Cortex	0.21225	0.24140
ENSG000	chr5	PCDHGB2	Protein coding	KNOWN	0.36812	3.4064	0.00065	0.10806	Frontal Cortex	0.21225	0.24567
ENSG000	chr1	ADCK3	Protein coding	KNOWN	-	-	0.00078	0.13758	Frontal Cortex	0.21383	0.27563
ENSG000	chr11	EFCAB4A	Protein coding	KNOWN	-	-	0.00080	0.46011	Frontal Cortex	0.21383	0.27563
ENSG000	chr13	LINC00443	lincRNA	KNOWN	-	-	0.00084	0.13157	Frontal Cortex	0.21383	0.27563
ENSG000	chr2	BARD1	Protein coding	KNOWN	-	-	0.00094	0.20376	Frontal Cortex	0.21680	0.28320
ENSG000	chr17	FDXR	Protein coding	KNOWN	-	-	0.00106	0.13251	Cortex	0.35437	0.28320
ENSG000	chr17	QRICH2	Protein coding	KNOWN	1.44595	3.2725	0.00106	0.44183	Frontal Cortex	0.21680	0.28320
ENSG000	chr14	TMEM253	Protein coding	KNOWN	-	-	0.00107	0.23795	Cortex	0.35437	0.28320
ENSG000	chr9	KIF12	Protein coding	KNOWN	-	-	0.00108	0.41511	Frontal Cortex	0.21680	0.28320
ENSG000	chr16	NPIPP1	pseudogene	KNOWN	0.60147	3.2636	0.00109	0.18429	Frontal Cortex	0.21680	0.28320
ENSG000	chr2	ANKMY1	Protein coding	KNOWN	0.74492	3.2525	0.00114	0.22902	Cortex	0.35437	0.28320
ENSG000	chr8	TRAPPC9	Protein coding	KNOWN	1.14127	3.2495	0.00115	0.35121	Cortex	0.35437	0.28320
ENSG000	chr13	DHRS12	Protein coding	KNOWN	-	-	0.00119	0.26722	Frontal Cortex	0.22295	0.28365
ENSG000	chr10	ATOH7	Protein coding	KNOWN	-	-	0.00127	0.20934	Frontal Cortex	0.22600	0.29376
ENSG000	chr2	CRYGA	Protein coding	KNOWN	0.73737	3.1905	0.00141	0.23111	Frontal Cortex	0.23990	0.31807
ENSG000	chr11	PANX1	Protein coding	KNOWN	-	-	0.00154	0.15792	Cortex	0.44332	0.33741
ENSG000	chr7	ZNF736	Protein coding	KNOWN	0.50305	3.1220	0.00179	0.16112	Cortex	0.45139	0.36445
ENSG000	chr7	PUS7	Protein coding	KNOWN	1.23314	3.1205	0.00180	0.39516	Frontal Cortex	0.27967	0.36445
ENSG000	chr11	LDHAL6A	Protein coding	KNOWN	0.99369	3.1192	0.00181	0.31856	Frontal Cortex	0.27967	0.36445
ENSG000	chr17	CLDN7	Protein coding	KNOWN	-	-	0.00192	0.13079	Cortex	0.45139	0.37555
ENSG000	chr7	C7orf55	Protein coding	KNOWN	-	-	0.00196	0.17469	Frontal Cortex	0.29034	0.37555
ENSG000	chr14	CHURC1	Protein coding	KNOWN	-	-	0.00204	0.10124	Cortex	0.45139	0.38126
ENSG000	chr19	CEACAM19	Protein coding	KNOWN	-	-	0.00216	0.33488	Frontal Cortex	0.30679	0.39414
ENSG000	chr11	IFT46	Protein coding	KNOWN	0.73998	3.0552	0.00224	0.24219	Cortex	0.45139	0.40068
ENSG000	chr8	RP11-140I16.3	lincRNA	NOVEL	-	-	0.00231	0.42677	Cortex	0.45139	0.40201
ENSG000	chr4	FRAS1	Protein coding	KNOWN	1.19764	3.0408	0.00235	0.39384	Cortex	0.45139	0.40201
ENSG000	chr10	ASAH2	Protein coding	KNOWN	-	-	0.00251	0.10651	Frontal Cortex	0.34287	0.41912
ENSG000	chr16	GAS8	Protein coding	KNOWN	0.40840	2.9834	0.00285	0.13689	Cortex	0.45139	0.44398
ENSG000	chr15	RLBP1	Protein coding	KNOWN	-	-	0.00299	0.21269	Cortex	0.45139	0.44398
ENSG000	chr7	RP11-166O4.5	lincRNA	NOVEL	0.34858	2.9674	0.00300	0.11747	Cortex	0.45139	0.44398
ENSG000	chr19	ANKRD27	Protein coding	KNOWN	-	-	0.00302	0.26600	Cortex	0.45139	0.44398

ENSG000	chr2	ANKMY1	Protein coding	KNOWN	0.50418	2.9575	0.00310	0.17047	Frontal Cortex	0.39815	0.44398
ENSG000	chr12	DSTNP2	pseudogene	KNOWN	0.58833	2.9534	0.00314	0.19920	Frontal Cortex	0.39815	0.44398
ENSG000	chr17	MED24	Protein coding	KNOWN	0.66918	2.9531	0.00314	0.22660	Cortex	0.45139	0.44398
ENSG000	chr1	GS1-304P7.1	pseudogene	KNOWN	0.77482	2.9506	0.00317	0.26259	Cortex	0.45139	0.44398
ENSG000	chr5	CTC-419K13.1	lincRNA	NOVEL	0.43591	2.9458	0.00322	0.14797	Cortex	0.45139	0.44398
ENSG000	chr6	UST	Protein coding	KNOWN	-	-	0.00325	0.14492	Cortex	0.45139	0.44398
ENSG000	chr20	ZNF663P	pseudogene	KNOWN	0.74243	2.9265	0.00342	0.25368	Cortex	0.45139	0.44398
ENSG000	chr2	FAM110C	Protein coding	KNOWN	0.96940	2.9259	0.00343	0.33130	Frontal Cortex	0.41567	0.44398
ENSG000	chr17	ABHD17AP6	pseudogene	KNOWN	-	-	0.00351	0.25455	Frontal Cortex	0.41567	0.44398
ENSG000	chr3	RP11-446H18.1	pseudogene	KNOWN	1.74512	2.9121	0.00358	0.59925	Cortex	0.45139	0.44398
ENSG000	chr7	GTF2IP1	pseudogene	KNOWN	-	-	0.00359	0.14682	Cortex	0.45139	0.44398
ENSG000	chr20	WFDC2	Protein coding	KNOWN	-	-	0.00360	0.45245	Cortex	0.45139	0.44398
ENSG000	chr13	TMCO3	Protein coding	KNOWN	-	-	0.00367	0.44909	Cortex	0.45139	0.44398
ENSG000	chr6	UBE3D	Protein coding	KNOWN	0.78295	2.9042	0.00368	0.26958	Cortex	0.45139	0.44398
ENSG000	chr3	EOGT	Protein coding	KNOWN	0.43842	2.8878	0.00387	0.15181	Frontal Cortex	0.41678	0.44481
ENSG000	chr19	POLR2E	Protein coding	KNOWN	-	-	0.00391	0.19441	Frontal Cortex	0.41678	0.44481
ENSG000	chr8	UBR5	Protein coding	KNOWN	0.56018	2.8826	0.00394	0.19432	Frontal Cortex	0.41678	0.44481
ENSG000	chr19	ZNF320	Protein coding	KNOWN	0.44469	2.8778	0.00400	0.15452	Frontal Cortex	0.41678	0.44481
ENSG000	chr6	TUBE1	Protein coding	KNOWN	0.53597	2.8669	0.00414	0.18695	Cortex	0.45945	0.44481
ENSG000	chr3	UROC1	Protein coding	KNOWN	-	-	0.00431	0.12007	Frontal Cortex	0.41678	0.44481
ENSG000	chr14	CDH24	Protein coding	KNOWN	2.42892	2.8491	0.00438	0.85250	Cortex	0.45945	0.44481
ENSG000	chr7	ABCB8	Protein coding	KNOWN	-	-	0.00444	0.46988	Cortex	0.45945	0.44481
ENSG000	chr22	FAM227A	Protein coding	KNOWN	-	-	0.00447	0.18437	Cortex	0.45945	0.44481
ENSG000	chr19	CTD-2331H12.5	pseudogene	KNOWN	0.80188	2.8416	0.00448	0.28218	Cortex	0.45945	0.44481
ENSG000	chr11	SAAL1	Protein coding	KNOWN	0.45942	2.8389	0.00452	0.16182	Frontal Cortex	0.41678	0.44481
ENSG000	chr1	PSRC1	Protein coding	KNOWN	0.71790	2.8382	0.00453	0.25294	Cortex	0.45945	0.44481
ENSG000	chr9	C9orf72	Protein coding	KNOWN	-	-	0.00461	0.16881	Frontal Cortex	0.41678	0.44481
ENSG000	chr7	TRIM73	Protein coding	KNOWN	-	-	0.00466	0.26213	Cortex	0.45945	0.44481
ENSG000	chr13	SOHLH2	Protein coding	KNOWN	-	-	0.00469	0.10465	Cortex	0.45945	0.44481
ENSG000	chr7	TMEM176A	Protein coding	KNOWN	0.47492	2.8236	0.00474	0.16819	Frontal Cortex	0.41678	0.44481
ENSG000	chr17	TOP3A	Protein coding	KNOWN	-	-	0.00485	0.14245	Cortex	0.45945	0.44481
ENSG000	chr4	QRFPR	Protein coding	KNOWN	0.63308	2.8153	0.00487	0.22486	Frontal Cortex	0.41678	0.44481
ENSG000	chr7	RBM28	Protein coding	KNOWN	0.74771	2.8145	0.00488	0.26566	Cortex	0.45945	0.44481
ENSG000	chr19	PDCD5	Protein coding	KNOWN	-	-	0.00489	0.37334	Frontal Cortex	0.41678	0.44481
ENSG000	chr16	DNAAF1	Protein coding	KNOWN	0.67462	2.8108	0.00494	0.24001	Frontal Cortex	0.41678	0.44481
ENSG000	chr2	EPB41L5	Protein coding	KNOWN	-	-	0.00496	0.29029	Cortex	0.45945	0.44481
ENSG000	chr10	TRDMT1	Protein coding	KNOWN	0.56164	2.8050	0.00503	0.20022	Frontal Cortex	0.41678	0.44481
ENSG000	chr15	RAB27A	Protein coding	KNOWN	0.31372	2.7967	0.00516	0.11217	Frontal Cortex	0.41678	0.44481
ENSG000	chr22	SLC25A1	Protein coding	KNOWN	-	-	0.00517	0.22925	Frontal Cortex	0.41678	0.44481
ENSG000	chr3	OR7E29P	pseudogene	KNOWN	-	-	0.00526	0.24493	Cortex	0.45945	0.44481
ENSG000	chr12	SP1	Protein coding	KNOWN	0.61233	2.7844	0.00536	0.21991	Cortex	0.45945	0.44481
ENSG000	chr6	CCDC170	Protein coding	KNOWN	0.57553	2.7838	0.00537	0.20673	Frontal Cortex	0.41678	0.44481
ENSG000	chr2	CREG2	Protein coding	KNOWN	-	-	0.00537	0.40249	Cortex	0.45945	0.44481
ENSG000	chr5	CTC-534A2.2	Protein coding	KNOWN	-	-	0.00540	0.18770	Frontal Cortex	0.41678	0.44481
ENSG000	chr13	SOHLH2	Protein coding	KNOWN	-	-	0.00552	0.11307	Frontal Cortex	0.41678	0.44481
ENSG000	chr13	FAM58DP	pseudogene	KNOWN	0.32148	2.7716	0.00557	0.11599	Cortex	0.45945	0.44481
ENSG000	chr1	REN	Protein coding	KNOWN	-	-	0.00559	0.39456	Cortex	0.45945	0.44481
ENSG000	chr7	RP9P	pseudogene	KNOWN	-	-	0.00566	0.28118	Cortex	0.45945	0.44481
ENSG000	chr12	ZNF140	Protein coding	KNOWN	-	-	0.00567	0.19988	Cortex	0.45945	0.44481
ENSG000	chr3	KLHL24	Protein coding	KNOWN	-	-	0.00599	0.28877	Cortex	0.46743	0.46282
ENSG000	chr13	LINC00551	lincRNA	NOVEL	-	-	0.00612	0.15604	Frontal Cortex	0.45267	0.46282
ENSG000	chr7	MGAM	Protein coding	KNOWN	-	-	0.00613	0.19369	Cortex	0.46743	0.46282
ENSG000	chr7	RP11-667F9.1	pseudogene	KNOWN	-	-	0.00614	0.29431	Cortex	0.46743	0.46282
ENSG000	chr7	PHBP15	pseudogene	KNOWN	0.44702	2.7345	0.00624	0.16347	Cortex	0.46743	0.46282
ENSG000	chr6	FUT9	Protein coding	KNOWN	0.61790	2.7338	0.00626	0.22602	Frontal Cortex	0.45333	0.46282
ENSG000	chr1	CROCCP2	lincRNA	NOVEL	0.59739	2.7308	0.00631	0.21875	Cortex	0.46743	0.46282
ENSG000	chr17	DLG4	Protein coding	KNOWN	-	-	0.00662	0.26580	Frontal Cortex	0.46693	0.48065
ENSG000	chr16	SPIRE2	Protein coding	KNOWN	0.58049	2.7081	0.00676	0.21435	Frontal Cortex	0.46693	0.48661
ENSG000	chr7	STYXL1	Protein coding	KNOWN	-	-	0.00685	0.18189	Frontal Cortex	0.46693	0.48825

ENSG000	chr7	GPNMB	Protein coding	KNOWN	-	-	0.00697	0.12972	Cortex	0.48926	0.48825
ENSG000	chr7	ZBED6CL	Protein coding	KNOWN	-	-	0.00697	0.22124	Frontal Cortex	0.46693	0.48825
ENSG000	chr2	RMND5A	Protein coding	KNOWN	1.53765	2.6903	0.00713	0.57155	Cortex	0.48926	0.49299
ENSG000	chr9	GPSM1	Protein coding	KNOWN	0.63345	2.6848	0.00725	0.23594	Cortex	0.48926	0.49299
ENSG000	chr6	C6orf47	Protein coding	KNOWN	0.70972	2.6832	0.00729	0.26449	Frontal Cortex	0.46772	0.49299
ENSG000	chr8	RP11-163N6.2	lincRNA	NOVEL	-	-	0.00737	0.32291	Frontal Cortex	0.46772	0.49299
ENSG000	chr3	LTF	Protein coding	KNOWN	0.58089	2.6790	0.00738	0.21682	Frontal Cortex	0.46772	0.49299
ENSG000	chr7	PTPRN2	Protein coding	KNOWN	1.33012	2.6716	0.00754	0.49785	Cortex	0.48926	0.49299
ENSG000	chr1	TDRD5	Protein coding	KNOWN	0.34731	2.6699	0.00758	0.13007	Frontal Cortex	0.47214	0.49299
ENSG000	chr15	RP11-561C5.4	pseudogene	KNOWN	-	-	0.00766	0.10351	Cortex	0.48926	0.49299
ENSG000	chr13	TPTE2P5	pseudogene	KNOWN	-	-	0.00768	0.23778	Cortex	0.48926	0.49299
ENSG000	chr22	MORC2	Protein coding	KNOWN	-	-	0.00772	0.19979	Cortex	0.48926	0.49299
ENSG000	chr22	CLTCL1	Protein coding	KNOWN	0.39208	2.6634	0.00773	0.14721	Cortex	0.48926	0.49299
ENSG000	chr15	SCAND2P	pseudogene	KNOWN	-	-	0.00783	0.28644	Cortex	0.48926	0.49354
ENSG000	chr1	HMGCL	Protein coding	KNOWN	-	-	0.00791	0.18312	Cortex	0.48926	0.49354
ENSG000	chr12	SPSB2	Protein coding	KNOWN	0.35690	2.6549	0.00793	0.13442	Cortex	0.48926	0.49354
ENSG000	chr12	CHPT1	Protein coding	KNOWN	-	-	0.00800	0.12369	Frontal Cortex	0.48141	0.49438
ENSG000	chr17	MED24	Protein coding	KNOWN	0.61537	2.6455	0.00815	0.23260	Frontal Cortex	0.48141	0.49558
ENSG000	chr22	VPREB3	Protein coding	KNOWN	-	-	0.00818	0.13211	Frontal Cortex	0.48141	0.49558
ENSG000	chr8	RPS20	Protein coding	KNOWN	-	-	0.00827	0.30425	Frontal Cortex	0.48141	0.49558
ENSG000	chr19	ZNF30	Protein coding	KNOWN	-	-	0.00859	0.21702	Cortex	0.48926	0.49558
ENSG000	chr4	PACRGL	Protein coding	KNOWN	0.28371	2.6271	0.00861	0.10799	Frontal Cortex	0.48662	0.49558
ENSG000	chr16	RP11-314O13.1	lincRNA	NOVEL	-	-	0.00864	0.33487	Frontal Cortex	0.48662	0.49558
ENSG000	chr9	CDC20P1	pseudogene	KNOWN	0.58666	2.6248	0.00866	0.22350	Cortex	0.48926	0.49558
ENSG000	chr11	LDHAL6A	Protein coding	KNOWN	0.64251	2.6224	0.00872	0.24500	Cortex	0.48926	0.49558
ENSG000	chr7	RP11-638I8.1	lincRNA	NOVEL	-	-	0.00873	0.34907	Cortex	0.48926	0.49558
ENSG000	chr1	RP1-79C4.4	lincRNA	NOVEL	-	-	0.00877	0.15503	Cortex	0.48926	0.49558
ENSG000	chr7	POM121C	Protein coding	KNOWN	-	-	0.00885	0.11622	Cortex	0.48926	0.49558
ENSG000	chr7	AMZ1	Protein coding	KNOWN	1.24710	2.6173	0.00886	0.47646	Frontal Cortex	0.49120	0.49558
ENSG000	chr1	CD164L2	Protein coding	KNOWN	0.40455	2.6152	0.00891	0.15469	Cortex	0.48926	0.49558
ENSG000	chr1	HPCA	Protein coding	KNOWN	1.16098	2.6106	0.00903	0.44470	Cortex	0.48926	0.49558
ENSG000	chr7	STAG3L1	pseudogene	KNOWN	-	-	0.00906	0.21395	Cortex	0.48926	0.49558
ENSG000	chr1	LPPR5	Protein coding	KNOWN	2.29462	2.6084	0.00909	0.87968	Cortex	0.48926	0.49558

[1] S.E. = Standard error

[2] FDR_T = Tissue-specific false discovery rate

[3] FDR_O = Overall false discovery rate

Supplementary Table 3. Results of the linear regressions performed to compare MMN performance between patients and controls. MMN Amplitude (μV) was measured at the Fz electrode. All analyses were adjusted for of age, gender and MMN lab/electroencephalography machine. Related to Table 2.

Dataset	Patients vs. controls			
	Intercept	**Coefficient**	**Standard Error**	**p-value**
London	-3.66	0.66	0.22	0.003
Harvard	-4.62	-0.01	0.79	0.99
Maryland	-2.246	0.48	0.17	0.006
Whole sample	-3.84	0.697	0.13	3.46×10^{-08}

Reference group: controls
Effect group: patients

Supplementary Tables 4 A-D: Quality control of typed genotypes in each dataset (related to Genetic data collection and processing; STAR Methods).

A

ORIGINAL DATASET					
London		**Harvard**		**Maryland**	
Samples	**SNPs**	**Samples**	**SNPs**	**Samples**	**SNPs**
5602	929556	1692	719665	429	2335809

B

SAMPLE FILTERS						
	London		**Harvard**		**Maryland**	
Filter	**Criteria**	**Loss**	**Criteria**	**Loss**	**Criteria**	**Loss**
Sex mismatch	remove	57	remove	4	remove	0
Inbreeding	<-0.076 / > 0.076	70	<-0.1 / > 0.1	31	<-0.15 / > 0.15	12
Missingness	<2%	214	<5%	40	<5%	5
Duplicates	0.95 IDB	70	0.95 IDB	15	0.95 IDB	1
Mendelian errors	--	--	5%	0	--	--
Genetic Ancestry	outlier	356	--	--	--	--

C

SNP FILTERS						
	London		**Harvard**		**Maryland**	
Filter	**Criteria**	**Loss**	**Criteria**	**Loss**	**Criteria**	**Loss**
Missingness	>5%	11610	>5%	17165	>5%	986
Non-autosomal CHR	remove	38895	remove	20313	remove	55038
HI (p-value)	$< 1e^{-6}$	2404	$< 1e^{-6}$	14863	$< 1e^{-6}$	26984
MAF	<2%	145097	<1%	43442	<1%	462238
Mendelian errors	4 errors	26585	10%	100	NA	NA
Cluster plots	poor genotyping	9499	--	--	--	--

D

Quality Controlled Dataset					
London		**Harvard**		**Maryland**	
Samples	**SNPs**	**Samples**	**SNPs**	**Samples**	**SNPs**
4835	691252	1602	627550	411	1799738

Supplementary tables 5 A-C: Quality control of imputed genotypes in each dataset

A

ORIGINAL DATASET					
London		**Harvard**		**Maryland**	
Samples	**SNPs**	**Samples**	**SNPs**	**Samples**	**SNPs**
4835	39131578	1602	39131578	411	39131578

B

SNP FILTERS						
	London		**Harvard**		**Maryland**	
Filter	**Criteria**	**Loss**	**Criteria**	**Loss**	**Criteria**	**Loss**
INFO score	< 0.8	28048155	< 0.8	20351179	< 0.8	13630162
> 3 alleles	remove	9388	remove	15025	remove	29431
SNP position issues	remove	787	remove	15102	remove	24105
Missingness	> 5%	359398	> 5%	255007	> 5%	145213
HWE	$<1e^{-6}$	3803	$<1e^{-6}$	160771	$<1e^{-6}$	111221
MAF	< 1%	4246037	< 1%	11070085	<1%	15080028
Mendelian errors	10%	21	10%	2404	NA	NA
Case vs con missingness	<0.000001	10685	--	--	--	--

C

Quality Controlled Dataset					
London		**Harvard**		**Maryland**	
Samples	**SNPs**	**Samples**	**SNPs**	**Samples**	**SNPs**
4835	6454103	1602	7258616	411	10122483

Supplementary Table 6 A. Groupings of brain RNASeq samples from the BrainSpan Atlas by brain region. Related to neurodevelopmental enrichment analyses (STAR methods).

Brain structure	Samples	Brain region	Samples	Subjects	Cortex?	Samples	Subjects
Anterior (rostral) cingulate (medial prefrontal) cortex	32	Cingulate cortex	32	32	yes	361	42
Dorsolateral prefrontal cortex	35	Frontal cortex	127	38	yes		
Orbital frontal cortex	31						
Primary motor cortex (area M1, area 4)	26						
Ventrolateral prefrontal cortex	35						
Occipital neocortex	2	Occipital cortex	35	35	yes		
Primary visual cortex (striate cortex, area V1/V17)	33						
Parietal neocortex	2	Parietal cortex	66	35	yes		
Posteroventral (inferior) parietal cortex	33						
Primary motor-sensory cortex (samples)	5						
Primary somatosensory cortex (area S1, areas 3, 1, 2)	26						
Inferolateral temporal cortex (area Tev, area 20)	34	Temporal cortex	101	40	yes		
Posterior (caudal) superior temporal cortex (area 22c)	36						
Primary auditory cortex (core)	31						
Cerebellar cortex	29	Cerebellum	32	32	no	154	40
Cerebellum	3						
Dorsal thalamus	5	Diencephalon	29	29	no		
Mediodorsal nucleus of thalamus	24						
Amygdaloid complex	33	Subcortical	93	37	no		
Hippocampus (hippocampal formation)	32						
Striatum	28						

Supplementary Table 6B. Groupings of brain RNASeq samples from the BrainSpan Atlas by age. Related to neurodevelopmental enrichment analyses (STAR Methods).

Stage	Age	Subjects	Samples	Age group	Subjects	Samples
PRE-NATAL	8 pcw[a]	1	12	8 - 12 pcw	5	66
	9 pcw	1	9			
	12 pcw	3	45			
	13 pcw	3	44	13 - 16 pcw	6	83
	16 pcw	3	39			
	17 pcw	1	14	17 - 24 pcw	5	57
	19 pcw	1	11			
	21 pcw	2	16			
	24 pcw	1	16			
	25 pcw	1	1	25 - 37 pcw	4	22
	26 pcw	1	3			
	35 pcw	1	2			
	37 pcw	1	16			
POST-NATAL	4 months	3	33	4 months - 1 year	5	59
	10 months	1	10			
	1 years	1	16			
	2 years	1	12	2 - 4 years	4	44
	3 years	2	25			
	4 years	1	7			
	8 years	2	27	8 - 15 years	5	62
	11 years	1	14			
	13 years	1	16			
	15 years	1	5			
	18 years	1	13	18 - 23 years	4	59
	19 years	1	16			
	21 years	1	16			
	23 years	1	14			
	30 years	1	16	30 - 40 years	4	63
	36 years	1	16			
	37 years	1	16			
	40 years	1	15			

[a]pcw = post-conception weeks

Supplementary Table 7: Results of the bivariate GREML analyses performed with GCTA. Related to endophenotype ranking analysis (STAR Methods).

Phenotype	N	GCTA possible ?	Error	ERV	Heritability			Genetic correlation		
					Estimate	S.E.[a]	95% C.I.	rG	S.E.[a]	95% C.I.[b]
Digit Symbol	27	no	Variance-covariance matrix invertibility	NA	NA	NA	NA	NA	NA	NA
Digit Span Forward	72	yes	NA	0.41	0.83	0.37	[0.10; 1.56]	-1.00	1.43	[-3.80; 1.80]
IQ	324	no	Likelihood convergence	NA	NA	NA	NA	NA	NA	NA
Mismatch negativity	403	yes	NA	0.28	0.38	0.15	[0.09; 0.68]	1.00	0.22	[0.58; 1.42]
P300 Amplitude	510	yes	NA	0.36	0.64	0.17	[0.31; 0.97]	1.00	4.55	[-7.93; 9.93]
P300 Latency	515	no	Variance-covariance matrix invertibility	NA	NA	NA	NA	NA	NA	NA
Lateral ventricular volume	775	yes	NA	0.02	0.66	0.17	[0.35; 0.97]	-0.05	0.27	[-0.58; 0.48]
Whole brain volume	777	no	Likelihood convergence	NA	NA	NA	NA	NA	NA	NA
RAVLT delayed	2384	yes	NA	0.10	0.34	0.06	[0.22; 0.46]	-0.39	0.10	[-0.59; -0.19]
RAVLT immediate	2406	yes	NA	0.13	0.35	0.06	[0.23; 0.48]	-0.50	0.10	[-0.68; -0.31]
Block Design	3089	yes	NA	0.34	0.69	0.05	[0.59; 0.79]	-0.93	5.14	[-11.01; 9.15]

[a] S.E = Standard error
[b] C.I. = Confidence intervals
ERV = Endophenotype Ranking Value
RAVLT = Ray Auditory Verbal Learning Task

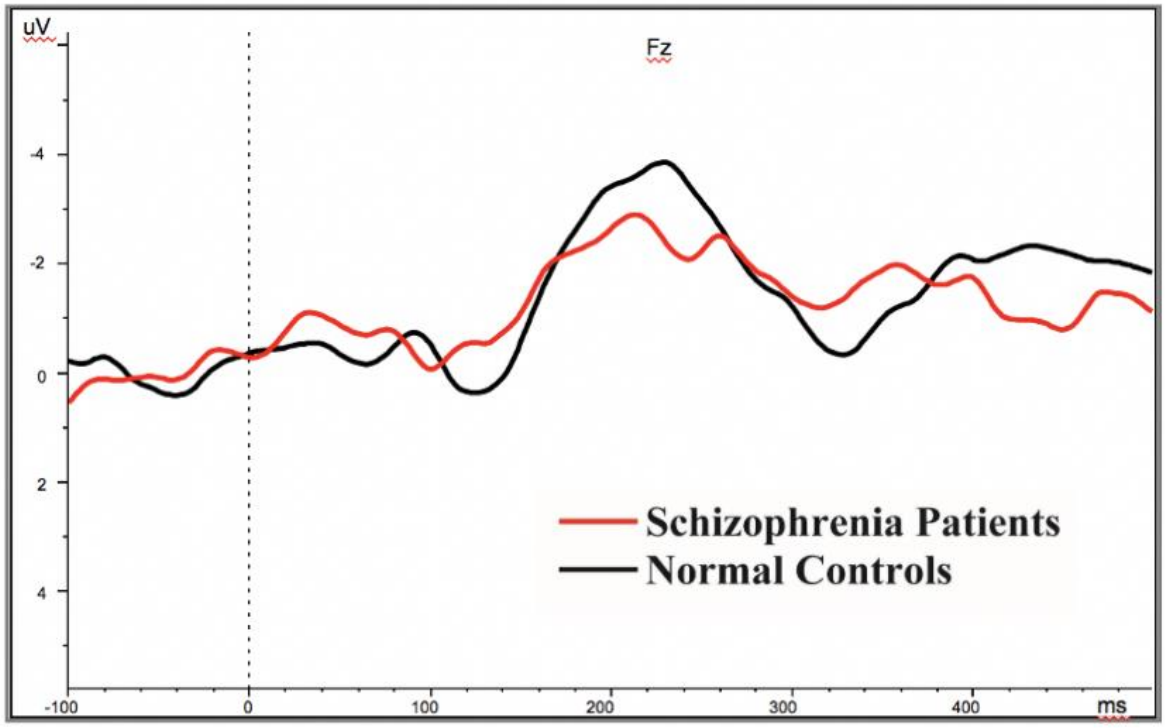
Supplementary Table 8. Mean mismatch negativity latency[b] at FZ (ms) in each of the datasets by group. Related to Table 2.

Sample	Patients	Controls	Relatives	Whole dataset
Maryland (*n* = 403)	190.9 ± 27.22[a]	180.33 ± 31.88	-	186.6 ± 29.63
Harvard (*n* = 66)	174.38 ± 33.07	198.36 ± 25.97	-	179.83 ± 33.0
PEIC (*n* = 100)	98.58 ± 19.69	100.54 ± 16.61	103.08 ± 14.67	100.75 ± 17.09

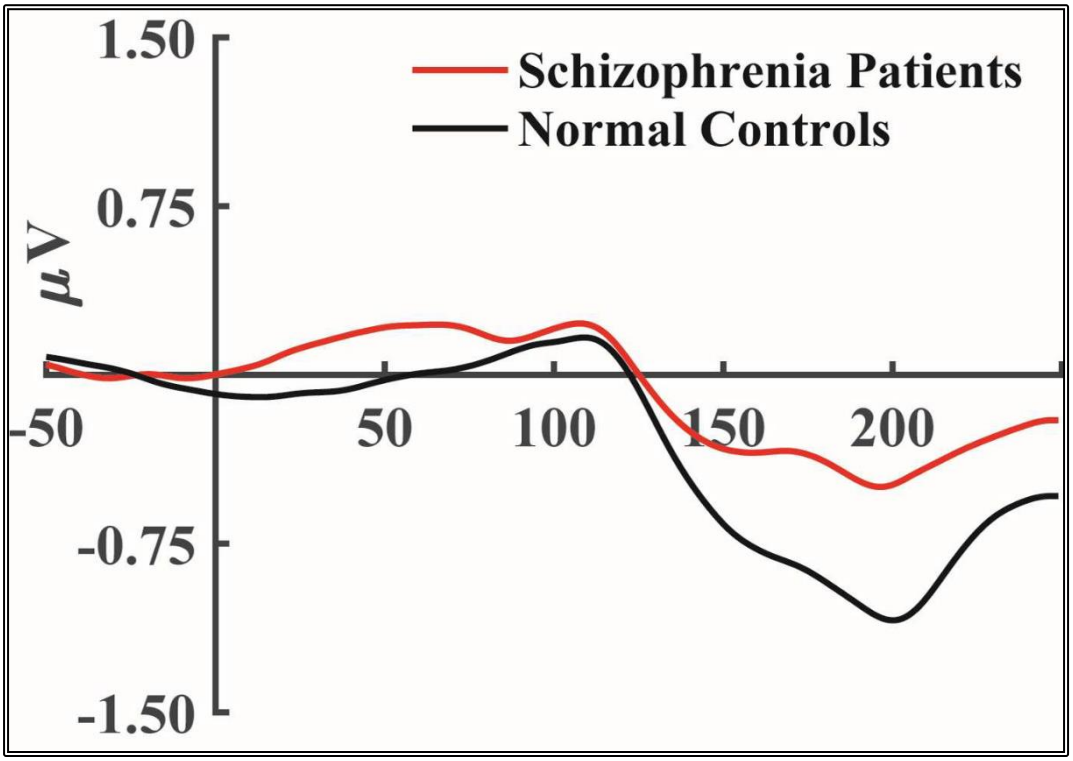
[a]Mean ± Standard deviation (in ms)

[b]These values are unadjusted for covariates

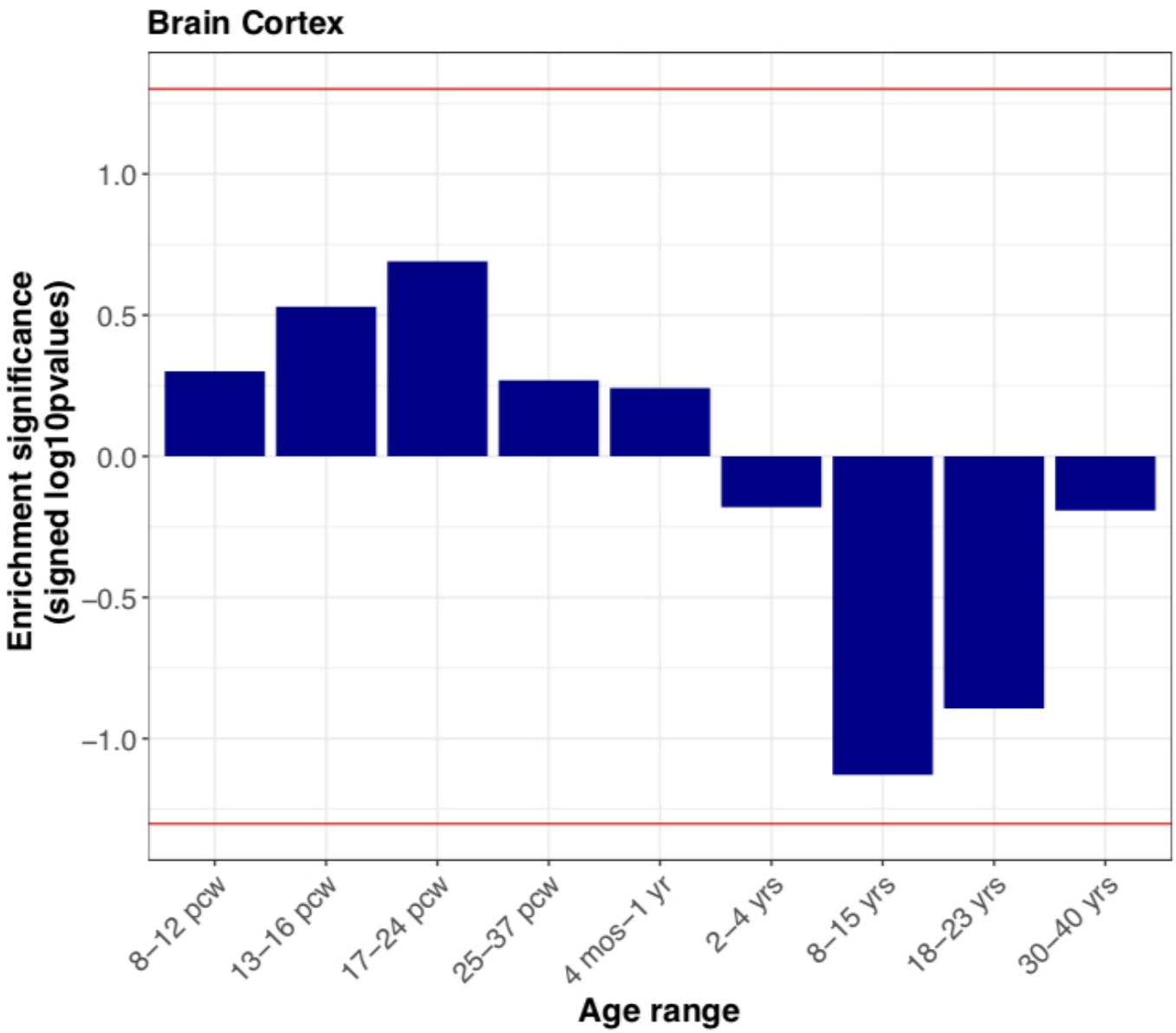
Supplementary Figure 1. MMN FZ grand average waveforms for patients (red) and controls (black) in the Harvard sample (*n* = 71). Related to Table 2.



Supplementary Figure 2. MMN FZ grand average waveforms for patients (red) and controls (black) in the Maryland sample (*n* = 403). Related to Table 2.



Supplementary Figure 3. Neurodevelopmental signature enrichment results for whole cortex. Related to Figure 3.



Chapter 2

Suppression of the inflammatory response in schizophrenia hiPSC-derived neural progenitors: A gene-environment interaction study

Abstract

Prenatal exposure to infection is an environmental risk factor for neurodevelopmental disorders such as schizophrenia. Inflammation in the maternal and foetal compartments, characterised by elevated cytokine levels, is thought to play an important role in this association. Such inflammatory effects compound with polygenic risk to 'tip the balance' towards developing schizophrenia. Exposure to the cytokines interferon-gamma (IFNγ) and interleukin-1 beta (IL-1β) triggers a foetal immune response – but how such environmental insults interact with a genetic background associated with schizophrenia and influence neurodevelopment is unknown. I hypothesised that developing neurons with a genetic predisposition for schizophrenia would respond differently to IFNγ or IL-1β exposure compared to those from controls. I tested this by assessing differential gene expression responses in human forebrain-lineage neural progenitor cells (NPCs) derived from induced pluripotent stem cells generated from three people with schizophrenia and three controls. The NPCs were treated for 24 hours with either 25ng/µl IFNγ or 10ng/µl IL-1β, after which RNA was extracted and sequenced. The analyses showed 3380 differentially expressed genes (DEGs) in IFNγ-treated control lines (compared to untreated controls), but only 1980 DEGs in IFNγ-treated patient cells (compared to untreated patient cells). There were 359 genes that responded significantly differently to IFNγ treatment in schizophrenia lines compared to controls, and pathway analysis of this comparison showed suppression of gene pathways related to antigen processing and synaptic transmission: most significantly, those involved in regulating the neuronal post-synaptic density and the presynapse. There were no differentially expressed genes in the IL-1β-treatment conditions, which may be because IL-1β receptors were minimally expressed in all six cell lines. Taken together, these results exemplify responses to immune insults that are altered in cells with a genetic predisposition for schizophrenia; in particular indicating that IFNγ elicits a reduced transcriptional response, especially of genes regulating synaptic transmission, in schizophrenia NPCs.

Introduction

Over the last three decades, there has been increasing evidence that exposure to infection, and the consequent activation of the immune response, is an environmental risk factor for neuropsychiatric disorders such as schizophrenia – especially so when immune activation occurs during prenatal development (Byrne et al., 2007; Estes & McAllister, 2016; Kepinska et al., 2020; Meyer, 2019; Warre-Cornish et al., 2020). A likely molecular contributor to this link between 'maternal immune activation' and schizophrenia is exposure of the developing foetal brain to pro-inflammatory cytokines (Garay et al., 2013; Gilmore et al., 2004; Warre-Cornish et al., 2020). Cytokines are small proteins that are released by cells – generally performing the function of cell signalling – and are particularly central to the immune system, where they primarily advance or suppress inflammation (Murphy et al., 2012). It is possible that cytokines can directly enter the foetal brain during early pregnancy, as the blood–brain barrier is not completely developed at this stage (Adinolfi, 1985). Here, chronically or acutely elevated levels of pro-inflammatory cytokines may lead to autoimmune damage (Baines et al., 2020; Ben-Reuven & Reiner, 2019; Jain et al., 2020; Lesh et al., 2018).

Two pro-inflammatory cytokines that appear to play a particularly important part in neurodevelopment are interferon gamma (IFNγ) (Lesh et al., 2018; Warre-Cornish et al., 2020) and interleukin 1 beta (IL-1β) (Crampton et al., 2012; Gilmore et al., 2004), both of which are elevated in plasma from people with schizophrenia (Lesh et al., 2018). Recent work in humans has shown increased serum levels of IL-1β in mothers of offspring who later develop psychosis (Allswede et al., 2020). This is congruent with animal studies showing offspring that are exposed to maternal immune activation and exhibit consequent behavioural deficits have elevated plasma levels of IL-1β (Mueller et al., 2021). A previous study from our group also demonstrated a significant influence of IFNγ stimulation of developing human neurons on expression of schizophrenia risk genes such as *ZNF804A* and *GRIN2A* (Warre-Cornish et al., 2020).

IFNγ plays a central role in the cellular response to viral infection, both in the short term – by triggering macrophages to destroy pathogens they may have engulfed (Kak et al., 2018; Murphy et al., 2012) – and in the long term – by facilitating a transcriptional 'memory' for known viruses (Kamada et al., 2018). It is emerging that IFNγ also performs several other functions in the body, even in the absence of infection. For example, IFNγ is involved in neuronal connectivity and social behaviour: Filiano et al. (2016) show (in mice) that IFNγ expression is associated with social deficits and hyperconnectivity in the frontal cortex. IL-1β is an important mediator of the innate immune response and induces fever in the presence of infection (Gilmore et al., 2004; Schroder & Tschopp, 2010). Like IFNγ, our knowledge of its roles beyond immunity are expanding, many of which draw a direct link to mechanisms that are affected in schizophrenia. In the brain, IL-1β promotes long-term potentiation (Avital et al., 2003; Schneider et al., 1998) as well as activating the kynurenine pathway that mediates glutamate neurotransmission (Muller et al., 2013), and is an important mediator of sickness behaviours (e.g., reduced appetite, inactivity, social avoidance) (Anforth et al., 1998). On a cellular level, IL-1β exposure significantly reduces the dendritic arborisation of rat cortical neurons (Gilmore et al., 2004).

However, the impact of such immune insults varies between individuals (Carlezon et al., 2019; Meyer, 2019; Mueller et al., 2021). The 'two-hit' hypothesis of schizophrenia suggests that an amalgam of genetic risk and environmental insult is necessary to alter neurodevelopment enough to ultimately precipitate the symptoms of the full-fledged illness (Feigenson et al., 2014; van Os et al., 2008). Any environmental influences (e.g., infection) will inevitably interact with the genetic makeup of the exposed foetus, so for a full picture of how they influence schizophrenia susceptibility, it is imperative to understand these gene-environment interactions. A precise aetiology of this sort is particularly necessary for polygenic, heterogeneous disorders like schizophrenia. The literature on gene-environment interactions in schizophrenia in the case of infection exposure is limited, and largely focuses on specific

molecular components – calling for global, unbiased, exploratory studies that use RNA sequencing (reviewed by (Ayhan et al., 2016)).

Importantly, if there are individual differences in human responses to immune activation due to genetic variability, there will certainly be differences in such responses between human and animal systems, given that they are even more genetically divergent. It is therefore particularly beneficial for this kind of precision-seeking gene-environment interaction study to be able to experimentally leverage a human system. It has, of course, been impossible to experimentally test the direct impact of inflammatory cytokines on the brains of human foetuses. However, recent developments in stem cell biology have offered an ethically sound way around this challenge. Human induced pluripotent stem cells (hiPSCs) can now be reprogrammed from adult hair samples (Aasen & Izpisua Belmonte, 2010; Petit et al., 2012; Takahashi & Yamanaka, 2006) and subsequently differentiated into cortical neural progenitor cells (NPCs) and neurons (Chambers et al., 2009; Warre-Cornish et al., 2020). These hiPSC-derived NPCs retain the genetic makeup of the donor (Adhya et al., 2020; Hoffman et al., 2017). However, having been differentiated from stem cells, they are thought to be of foetal maturity, and are seen to recapitulate the hallmarks of early neurodevelopment (Adhya et al., 2020; Brennand et al., 2015; Brennand & Gage, 2012; Kathuria et al., 2018; Shum et al., 2020; Warre-Cornish et al., 2020). This makes hiPSC-NPCs ideal *in vitro* models in which to study gene-environment interactions and test the neurodevelopmental hypothesis of schizophrenia (Hoffman et al., 2017). Warre-Cornish et al. (2020) showed that exposure of control NPCs to IFNγ induced a 'priming' effect such that, once the NPCs had matured into neurons, re-exposure to IFNγ elicited a 45% increase in transcription compared to un-primed neurons. This indicates that immune insults at this early neural progenitor stage can have a significant and enduring impact on the structure and function of neurons they beget. Experiments in animal models have also shown that exposure to inflammatory cytokines alters proliferation and differentiation of neural progenitors (Baines et al., 2020; Crampton et al., 2012). I therefore considered

this an ideal model in which to examine how the brain reacts to cytokine exposure at the earliest neurodevelopmental stage. For this study, induced cortical neural progenitors with forebrain identity are used, as there is extensive evidence of prefrontal cortical abnormalities in patients with schizophrenia (Broadbelt et al., 2002; Gilmore et al., 2004; Ranlund et al., 2016).

The aim of the current study is therefore to understand how specific cytokines implicated in the association between maternal immune activation and schizophrenia risk impact on early cortical neural progenitors. This is in order to identify potential molecular mechanisms that can explain this association in a human model system. I hypothesise that NPCs derived from patients with schizophrenia will respond differently to IFNγ and IL-1β compared to healthy cells. If so, this may shed light on the mechanisms by which maternal immune activation increases the risk of developing schizophrenia in those with genetic backgrounds that confer susceptibility.

Methods

Collaboration statement

For this study, I used human induced pluripotent stem cells (hiPSCs) that were reprogrammed from keratinocytes by other experimenters (primarily lab technicians Matthew Reid and Roland Nagy). These experimenters also collected the hair samples from participants. I cultured these cells, differentiated them into neural progenitors and extracted RNA, which was sent for sequencing by GeneWiz Ltd. I was also responsible for statistical analysis and write-up.

Participants

This study included hiPSC lines derived from six participants: three patients diagnosed with schizophrenia (schizophrenia lines: 138_SZM_09, 044_SCZ_04 and 115_SCZ_01) and three healthy donors with no history of psychiatric illness (control lines: M1_CTR_04, M2_CTR_42, M3_CTR_36S). Participants were recruited as part of the Patient iPSCs for Neurodevelopmental Disorders (PiNDs) study (REC No 13/LO/1218). Patients with schizophrenia who contributed hair samples were recruited at the Maudsley Hospital, London. The collection of data used for this research was approved by the NHS Research Ethics Committee at the South London and Maudsley (SLaM) NHS Research and Development Office. All participants gave written informed consent before contributing to the study.

Measures

Clinical Assessments

To confirm a DSM-V diagnosis of paranoid schizophrenia, participants were assessed by a psychiatrist or trained researcher using the following scales: the Positive and Negative Syndrome Scale (Kay et al., 1987) and the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (Endicott & Spitzer, 1978). Healthy controls were selected on the basis of having no history of psychiatric disorders.

Procedure

Reprogramming of keratinocytes

Hair root samples were collected by plucking occipital scalp hair (~10+ roots per participant) and submerging these in Mouse Embryonic Fibroblast medium containing 50ug/ml Gentamycin and 15mM HEPES buffer (Gibco). The roots were then transferred to Geltrex™-coated 4-well plates (ThermoFisher), and outgrowth promoted, by supplementing with hair medium (Dulbecco's Modified Eagle's Medium (DMEM) Advanced (Sigma Aldrich), GlutaMAX™ (ThermoFisher), 10% FBS (Clonetech), HEPES buffer and Gentamycin), to establish primary keratinocytes. The keratinocytes were subsequently reprogrammed into human induced pluripotent stem cell (hiPSC) lines. This transformation was induced by introducing Sendai viruses encoding Yamanaka Factors (human OCT4, SOX2, KLF4 and C-MYC), using a CytoTune-iPS 2.0 Sendai expressing Reprogramming Kit (ThermoFisher, A16517). The treated keratinocytes were plated onto an irradiated MEF feeder layer (Millipore) and supplemented Epilife medium. After ten days, Epilife medium was exchanged for hES medium, which was comprised of KO-DMEM/F12 supplemented with 20% knock-out serum, non-essential amino acids, Glutamax, β-mercaptoethanol (all from Life Technologies) and bFGF (10 ng/ml; Peprotech). After two more weeks, reprogrammed colonies were selected and plated on Nunc multi-plates (Thermo Scientific) coated with Geltrex (Life technologies) and supplemented with E8 media (Life Technologies). Successful reprogramming was validated as described in previous studies (Cocks et al., 2014; Kathuria et al., 2018; Shum et al., 2020). Pluripotency of all hiPSCs was confirmed by immunocytochemistry showing differentiation of embryoid bodies into the three characteristic germ layers (Boulting et al., 2011; Chambers & Tomlinson, 2009; International Stem Cell Initiative et al., 2007; Sheridan et al., 2012), and PluriTest analysis of Illumina HT12v4 transcriptome array data (www.pluritest.org) (Muller et al., 2011). Alkaline phosphatase activity was further used to assess the pluripotency of hiPSCs using an

alkaline phosphatase expression kit (Milipore). Genome integrity of hiPSC lines was assessed by an Illumina Human CytoSNP-12v2.1 beadchip array and analysed using KaryoStudio software (Illumina, San Diego, CA) and by G-banded karyotyping.

Maintenance of hiPSCs

The successfully reprogrammed hiPSCs were incubated in hypoxic conditions (5% CO2, 5% O_2) at 37°C and maintained in StemFlex™ media (Gibco) on 6-well NUNC™ plates (ThermoFisher) coated with Geltrex™ (ThermoFisher). Cells were passaged (at a ratio between 1:6 and 1:18) upon reaching 60-70% confluency. During passage, cells were washed with room temperature Hank's Balanced Salt Solution (HBSS) and incubated at 37°C with Versene (EDTA) solution (Lonza) for 3-5 minutes, then replated in new Geltrex™-coated NUNC™ plates.

Directed differentiation of hiPSCs

The six hiPSC lines used in this study were then differentiated into forebrain cortical neural progenitor cells (NPCs) by dual SMAD inhibition (Chambers et al., 2009). In preparation for neuralisation, hiPSCs were passaged onto 6-well NUNC™ plates coated with Geltrex™ at a 3:2 ratio and maintained under hypoxic conditions for ~24–48 hrs until they approached 100% confluence. Directed differentiation was then initiated by changing StemFlex™ medium to neuralisation medium containing N2:B27 (N2 medium and B27 medium at a 1:1 ratio) supplemented with 100 nM LDN193189 (Sigma Aldrich) and 10 µM SB431542 (Sigma Aldrich) for dual SMAD inhibition. N2 medium consisted of DMEM/F12 (Dulbecco's Modified Eagle's Medium/Nutrient Mixture F12 Ham; Sigma Aldrich), supplemented with 1X GlutaMAX™ and 1X N2 supplement (ThermoFisher). B27 medium consisted of Neurobasal® medium (ThermoFisher), 1X GlutaMAX™ (ThermoFisher) and 1X B27 supplement without vitamin A (ThermoFisher).

The neuralised cells were then incubated under normoxic conditions (37°C, 5% CO_2, 20% O_2). Neuralisation medium was replenished every 24 hours from day 0 to day 7. At the end of this 7-day neuralisation period, neuralisation medium was replaced with N2:B27 (without inhibitors), which was replenished every 24 hours from day 8 onwards. The neuralised cells were passaged four times: on day 7, day 12, day 15/16 and day 20/21. The passage procedure was, briefly, as follows: cells were washed with room temperature HBSS (ThermoFisher) and treated with Accutase (ThermoFisher) and incubated for 3–4 minutes at 37°C. The cells were then collected with the Accutase and mixed with room temperature DMEM/F12 (at a 2:1 ratio) and centrifuged at 1250 RPM for two minutes to separate the cells and Accutase. Cells were plated on new 6-well NUNC™ plates coated with Geltrex™. Passaging ratios were 1:1 for neural passaging 1 and 2, and 2:3 for neural passaging 3. To enhance cell survival, 10 µM protein kinase (ROCK) inhibitor (Sigma Aldrich), was added for 24 hours with the plating medium at each neural passage. After neural passage 3, cells were frozen in 10% DMSO (dimethyl sulfoxide). Cryovials were stored at -80°C for 24–48 hours in Mr. Frosty containers (to control freezing rate) before being transferred to liquid nitrogen.

For the final stages of neural passaging, cryovials were thawed in a 37°C water bath for 1 minute. The cell suspension was transferred to a 15 ml tube containing DMEM/F12 and centrifuged at 1250RPM for 2 minutes. The cell pellet was resuspended in 3ml of N2:B27 supplemented with 10µM ROCK inhibitor and plated in Geltrex™-coated 6-well NUNC™ plates. From this point on, the following inhibitors were added to the NPC media (to make N2:B27-FGF): 10ng/ml bFGF (basic Fibroblast Growth Factor; Peprotech), 100 µM β-mercaptoethanol (Life Technologies), 5µg/ml insulin (Life Technologies), 1X non-essential amino acids (Life Technologies), 200 µM ascorbic acid (Sigma Aldrich). The cells were then expanded at a 1:3 ratio (in 2–5 neural passages) to prepare three wells of each line (one for each experimental conditions).

Treatment with pro-inflammatory cytokines

NPCs were treated for ~24 hours in three treatment conditions: IFNγ, IL-1β and vehicle. Media was fully removed and replaced with 3 ml per well of treatment media (N2:B27-FGF, supplemented as follows). IFNγ wells were treated with 25ng/µl IFNγ (Abcam); the IL-1β wells with 10 ng/µl IL-1β (Abcam); and the control wells with vehicle (unsupplemented N2:B27-FGF media). After 24 hours, cells were lysed and collected in TRIzol® reagent (Thermo Fisher) and rapidly frozen on dry ice. The frozen samples were stored at -80°C until RNA extraction.

RNA extraction and sequencing

RNA was extracted from the eighteen samples in two batches (to ensure durations of exposure of each sample to extraction reagents were well controlled). Both batches of extractions were conducted on the same day, by the same experimenter. The batches were randomised for experimental group (batch 1: lines M1_CTR, M2_CTR, 138_SZM; batch 2: lines M3_CTR, 044_SCZ, 115_SCZ), using the RNeasy Plus Mini Kit (QIAGEN), according to the manufacturer's instructions. Extracted RNA was sent for sequencing at GENEWIZ® Ltd. Strand-specific, paired-end RNA sequencing with Poly(A) selection was conducted on the Illumina® NovaSeq platform, at a depth of ~30 million reads per sample.

Quality control of RNA sequence and gene expression data

Initial quality control checks of raw RNA sequence data were conducted using the FastQC software from Babraham Bioinformatics (www.bioinformatics.babraham.ac.uk/projects/fastqc). Sequence reads were then aligned to the latest version of the human reference genome (Hg38) using the STAR (Spliced Transcripts Alignment to a Reference) alignment tool (Baruzzo et al., 2017). The number of reads mapped onto each gene in Ensembl's gene annotations for hg38 (version 99) was counted using FeatureCounts (Liao et al., 2014). The distribution of $\log_{10}$-transformed counts-per-million (CPMs) were plotted. A threshold of $\log_{10}$CPM = 0.6 (CPM x $10^{0.6}$) was set (by visual inspection) for filtering out

lowly expressed genes in order to minimise technical noise and reduce the multiple-testing burden (Supplementary Figure 7). After applying that threshold, 15060 of 60642 genes were left for downstream analysis. TMM (trimmed mean of M-values)-normalization (Robinson & Oshlack, 2010) was then applied on the gene counts and the gene-expression values were $\log_2$ transformed and observational-level theoretical variances to use for precision-weighting were calculated using 'voom' (Law et al., 2014).

Statistical analysis

Differential gene expression

In order to evaluate potential sources of overall gene expression variation, Principal Component Analysis (PCA) was performed on the *voom*-transformed gene expression (Law et al., 2014), plotting the samples along the first three principal components (Supplementary Figure 2). The 'variancePartition' R package (Hoffman & Schadt, 2016) was used to estimate the contribution of variables to the variance in expression of each gene for the following: study subject, clinical group (schizophrenia/control), treatment condition (IFN-γ/IL-1β/vehicle), donor age, and the fraction of all RNA sequencing 'reads' that were mapped to genes (i.e., 'assigned percent').

To prepare the expression data for linear mixed effects modelling, the *voomWithDreamWeights* ('variancePartition' R package) was applied to the expression-level-filtered TMM-normalized counts. Linear mixed model regressions were then conducted using *dream* ('variancePartition'), which allows modelling of interindividual variability by adding individual identifiers as a random effect in the regression model, as shown below (Hoffman & Roussos, 2020; Hoffman & Schadt, 2016). I also included the 'assigned percent' for each sample as a covariate, as this can influence the calculation of gene expression. Participant age was not included as a covariate on the assumption that reprogramming samples to stem cells negates age-related effects (Mertens et al., 2015; Schrode et al., 2019). Age did seem to contribute to variation in gene expression in the variancePartition analysis (Supplementary

Figure 3), but this is may be due to noise as a result of the small size of the sample. All the participants were male, so gender was not included as a covariate. The final model with an interaction term between clinical group and treatment was as follows:

$$Y_i = \text{Group*Treatment} + \text{Assigned percent} + \text{Individual ID}$$

where "Group", "Treatment" and "Assigned percent" were fixed effects and "Individual ID" was a random intercept effect.

Using contrasts, the following differential gene expression signatures were generated:

A. **Vehicle-treated schizophrenia lines vs vehicle-treated control lines** (i.e., between schizophrenia and controls in cells treated with vehicle).
B. **IFNγ-treated control lines vs vehicle-treated control lines** (i.e., the effect of IFNγ stimulation on gene expression in the control cell lines).
C. **IFNγ-treated schizophrenia lines vs vehicle-treated schizophrenia lines** (i.e., the effect of IFNγ stimulation on gene expression in the schizophrenia cell lines).
D. **Interaction effect of IFNγ treatment in schizophrenia vs in controls** (i.e., how the expression of genes responds to IFNγ stimulation differently in patient lines compared to control cell lines).
E. **IL-1β -treated control lines vs vehicle-treated control lines** (i.e., the effect of IL-1β stimulation on gene expression in the control cell lines).
F. **IL-1β-treated schizophrenia lines vs vehicle-treated schizophrenia lines** (i.e., the effect of IL-1β stimulation on gene expression in the schizophrenia cell lines).
G. **Interaction effect of IL-1β treatment in schizophrenia vs in controls** (i.e., how the expression of genes responds to IL-1β stimulation differently in schizophrenia patient lines compared to control cell lines).

Approximation of residual degrees of freedom and subsequent calculation of moderated eBayes *t*-statistics was done using the Satterthwaite method in 'dream'.

Expression of cytokine receptors

In order to put the effects of IFN-gamma and IL-1beta on the NPCs into context, I extracted and visualized the expression of the genes that encode for their receptors: IFNGR1 and IFNGR2 for IFN-gamma and Il1R1, IL1RAP and IL1R2 for IL1-beta. To compare expression levels of these genes, FPKMs (fragments-per-kilobase-per-million) were calculated by normalizing the read counts by gene length (given as the sum of the lengths of all the exons in the gene model). This was done because the read count of each individual gene can be influenced by the length of the gene, which would not make a difference to group comparisons, but could do in gene-gene comparisons.

Gene set enrichment analysis

Our gene set enrichment analyses (GSEA) included 935 unique gene sets: 519 immune-related and 421 nervous-system/neural function related (5 overlapping). Of these, 135 were obtained from previous literature (Hall, Medway, et al., 2020; Pardiñas et al., 2018; Pocklington et al., 2015) and the remaining from either the Molecular Signature Database (HALLMARK and Gene Ontology biological process gene sets) or the pathway databases KEGG, PANTHER, Pathway Commons and Reactome. GSEA assesses whether genes belonging to specific pathways or predefined sets of genes are over-represented in the significant or peri-significant results of a differential expression analysis. A linear mixed effects regression-based competitive gene set enrichment approach was used with the GSEA tool (Subramanian et al., 2005) (Subramanian et al, 2005). GSEA was run on the seven signatures generated by the DGE analysis. The *fgsea* function of the R package 'fgsea' (Korotkevich et al., 2019) was applied, using the standardized Z-score obtained in the differential expression analysis to rank the genes and running

100,000 permutations. All gene sets containing fewer than five genes were excluded. I then selected gene sets with an FDR < 0.05 (multiple-testing correction is conducted within fgsea).

The resulting gene sets showed substantial constituent similarity (Supplementary Figure 4), so they were then clustered based on the overlap of the genes that belong to each gene set. This was done by calculating the Jaccard Similarity Index (which quantifies the intersection of two lists) between all pairs of significantly enriched gene sets and then applying a hierarchical clustering of gene sets based on the resulting dissimilarity matrix (1-Jaccard similarity). A cut-off of h=0.5 was then applied to the dendrograms to obtain clusters of significantly enriched gene sets (Supplementary Figure 5).

Results

Demographic and sample details

The demographic and clinical characteristics of the six participants can be seen in Table 1. All subjects were male and of White British background, except for one patient with a Black British background. Ages ranged from 33 to 55 years old. The patients were all diagnosed with (idiopathic) paranoid schizophrenia and controls were selected on the basis of having no history of neuropsychiatric disorders. One of the White British patients had a low polygenic risk score (PRS) for schizophrenia and a history of regular cannabis use, while the other had a high PRS for schizophrenia, with minimal use of cannabis. The Black British patient had a family history of schizophrenia and a deletion in the *NXRN1* region (PRS was not calculated for this patient due to unavailability of schizophrenia GWAS summary statistics for this ancestry group).

Table 1. Demographic and sample details

Cell line	Diagnosis	Year diagnosed	Medication	Age	Gender	Ethnicity	Risk profile	Reprogrammed by
044	Schizophrenia	2011	Risperidone	33	Male	White British	Low cannabis use, high PRS	Sendai virus
115	Schizophrenia	2010	Aripiprazol	43	Male	White British	High cannabis use, low PRS	Sendai virus
138	Schizophrenia	2008	Risperidone, Mirtazapine	39	Male	Black British	*NRXN1* deletion, family history of psychosis	Sendai virus
M1	Control	-	-	55	Male	White British	-	Lentivirus
M2	Control	-	-	35	Male	White British	-	Lentivirus
M3	Control	-	-	35	Male	White British	-	Sendai virus

[1]Percentage of all sequencing reads assigned to exons

Validation of hiPSCs and NPCs

All hiPSC lines passed quality control metrics, each showing differentiation into embryoid bodies with three characteristic germ layers and expression of pluripotency markers NANOG, OCT4, SSEA4 and TRA-1-81 (Supplementary Figure 1). For each participant, one clone was used for the NPC induction. All hiPSC lines successfully differentiated into NPCs as determined by immunostaining for known NPC markers βIII-tubulin and Nestin (Figure 1). For all individuals, genome-wide RNA-sequencing was generated from hiPSC-NPCs to compare transcriptional differences between patients with schizophrenia and control donors.

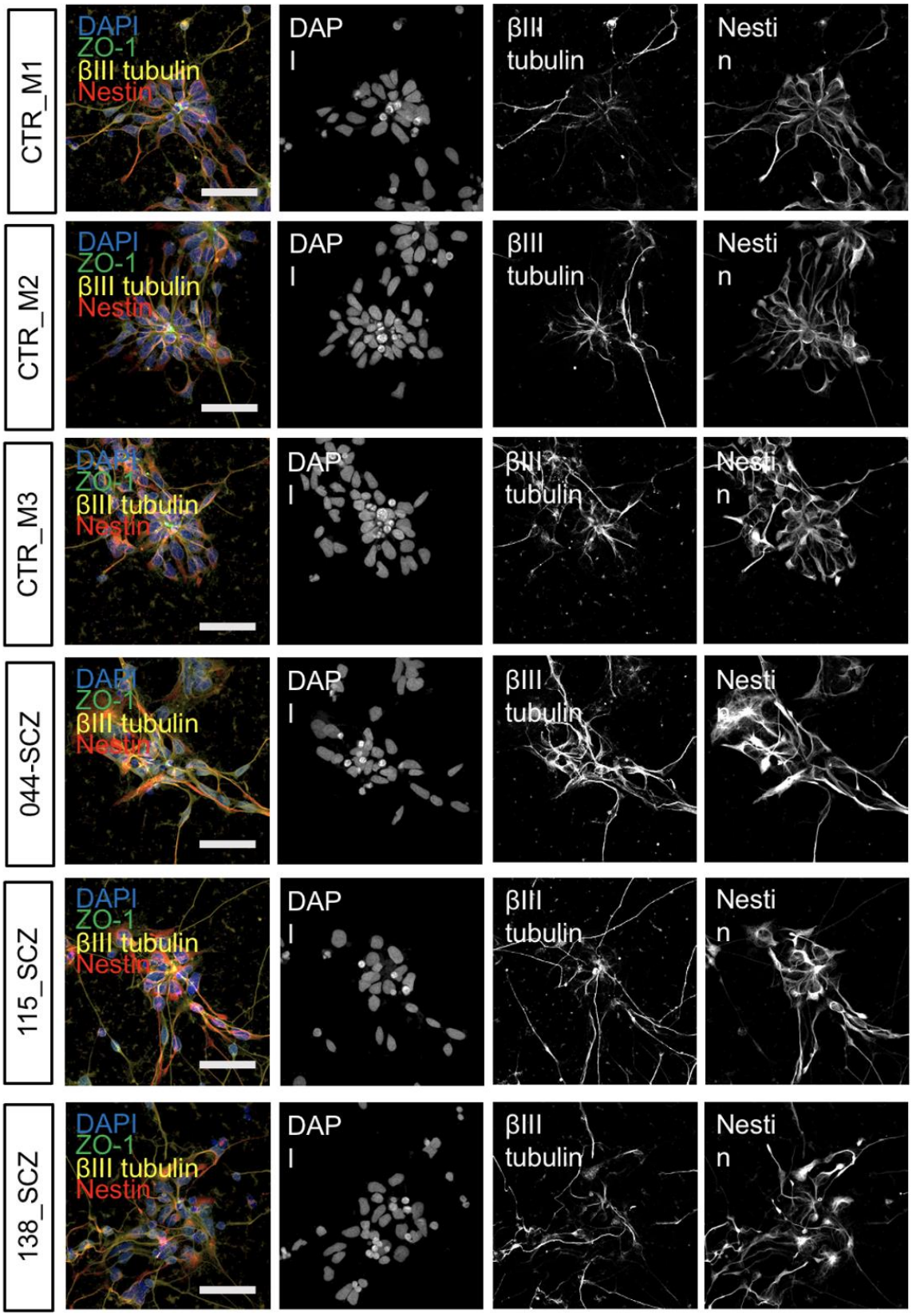


Figure 1. *Validation of neural progenitor cells.* Successful differentiation to neural progenitor state was confirmed by staining at Day 20 for NPC markers, Nestin and β-III-tubulin. DAPI was used for baseline nuclear staining. Scale bar = 50μm

Sources of variation in gene expression

In the variancePartition and principal component analysis (PCA) (by sample) of the gene expression data, I expected to see that the patient lines in this cohort would cluster together compared to control lines and that treatment with IFNγ or IL-1β would reduce this diagnosis-dependent clustering. There was some diagnosis-dependent clustering for PC2 and PC3, with more variability evident between patient lines. However, it appeared that the greatest source of variability, visible in PC1 (Supplementary Figure 2) as well as the variancePartition (Supplementary Figure 3) comparison, was from individual differences between the patients. The samples treated with IFNγ deviated slightly further from their corresponding untreated samples than the samples treated with IL-1β (evident in the PC2/PC3 plots), which is also reflected in the differential gene expression (DGE) analysis results: transcriptional responses were more significantly altered by IFNγ treatment than by IL-1β treatment. However, it is not clear from this analysis whether either treatment causes control lines to resemble schizophrenia lines more closely (potentially because the sample is underpowered, though it is also important to note that maternal immune activation is a generic 'priming' effect – i.e., the treatment-induced response is just as likely to overlap with autism-related gene sets).

Differential expression of genes and gene set enrichment analysis (GSEA)

Of the seven comparisons made, four yielded significant effects on gene expression: the effect of diagnosis (Signature A) and the three IFNγ treatment conditions (Signatures B-D). There were no differentially expressed genes (DEGs) as a result of IL1-β treatment. A full table of DEGs can be found in Supplementary Tables 3A-G and a full table of enrichment terms can be found in Supplementary Tables 4A-G. Immune related gene sets were among the top ten most significantly enriched for all seven signatures, and synaptic transmission related gene sets were among the top ten in four of the seven signatures. Details of DEGs and GSEA results for each signature are presented below. Figures 2-8 show

the top ten significantly enriched gene set clusters (the gene set with the lowest *p*-value in the most significant cluster is labelled).

Effect of schizophrenia diagnosis (Signature A)

I first assessed whether there were any differences in transcription between schizophrenia and control NPC lines (without treatment), at a False Discovery Rate (the *p*-value adjusted for multiple testing by the Benjamini-Hochberg correction method) of $FDR < 0.05$. In this comparison, there was only one significant DEG (Figure 2A): *AL132709.7* ($FDR = 0.0395$; logFC = -3.111), a human-specific lncRNA gene which was overexpressed in patient lines. It is possible the sample was underpowered to detect some valid DEG signals here, as there were 26 enriched gene pathways in untreated schizophrenia lines compared to untreated controls at the multiple-testing correction threshold of $FDR < 0.05$ and a cut-off of $h=0.5$ on the dendrograms of hierarchically clustered gene pathways (Supplementary Figure 5). The top five of these were enriched among upregulated genes in this comparison (Figure 2B), and the gene set with the lowest *p*-value in the most significantly enriched cluster was 'Lek2015 loss-of-function (90)' ($FDR =0.00098$; $NES = 1.36$; gene sets in cluster = 1; genes in gene set = 3007), which encodes 3007 genes that are intolerant to loss-of-function variants. Taken together with the fact that the Gene Ontology term 'regulation of ligase activity' – which regulates DNA ligase, responsible for DNA repair and replication – was also among the top five most overrepresented gene sets (Figure 2B), the results of this comparison point to a potential genomic fragility in schizophrenia NPCs compared to control NPCs.

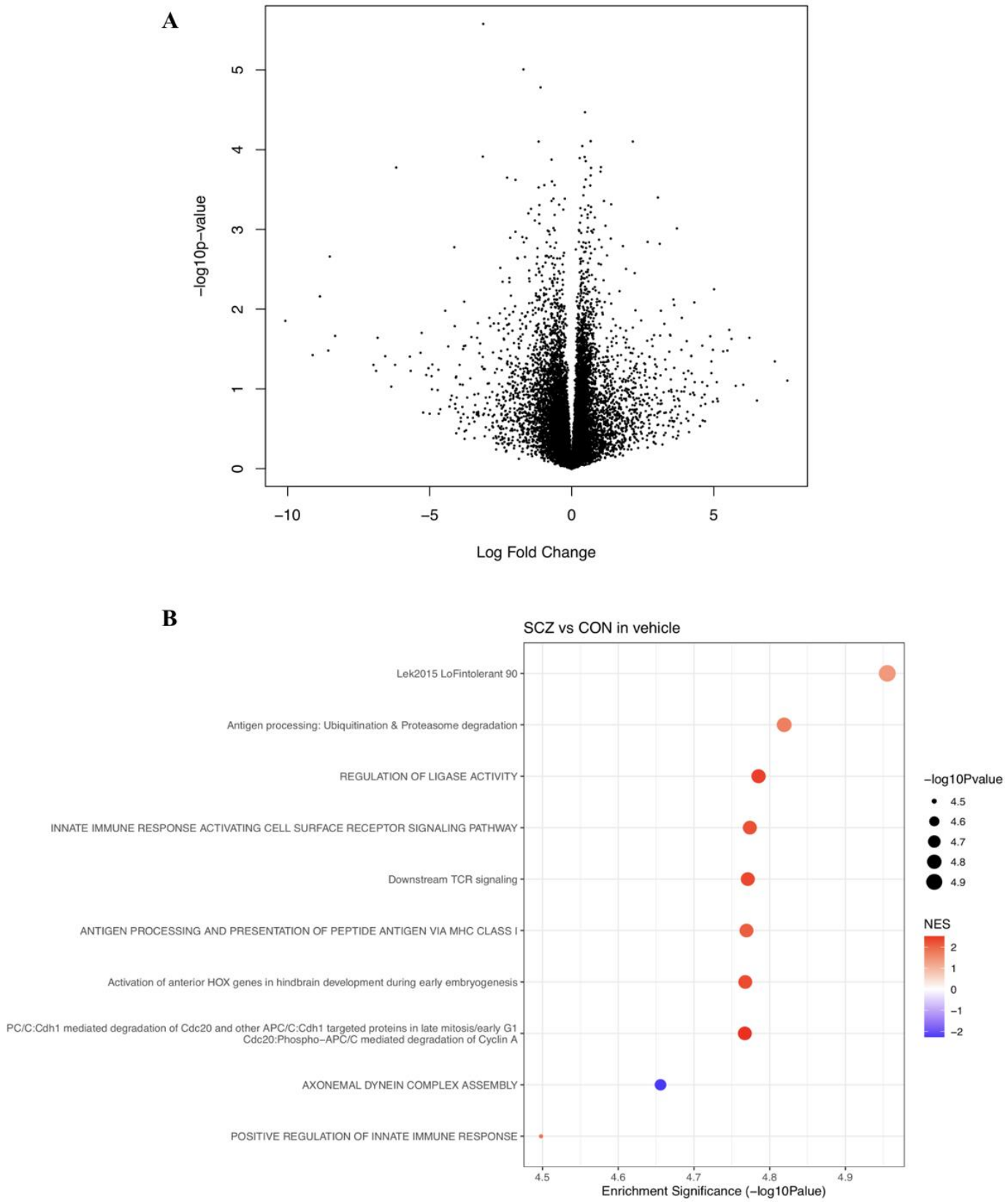


Figure 2. *Signature A.* **A.** The y-axis here shows statistical significance (-log10 p-value) of differential expression of genes in untreated cells from patient donors compared to gene expression in cells from untreated control donors. The x-axis shows the $\log_2$ fold change of expression of those genes in schizophrenia cell lines vs control cell lines. **B.** The top 10 significantly enriched gene set clusters (the gene set with the lowest p-value in each cluster is labelled on the x-axis). Data-points are sized according to significance (-log10 p-value) and coloured according to normalised enrichment score (NES), with blue indicating downregulation and red indicating upregulation.

Effect of IFNγ treatment in control cell lines (Signature B)

There was a significant effect of IFNγ treatment in control cell lines, with 3380 genes (out of the 15061 tested) differentially expressed in IFNγ-treated control cells compared to untreated control lines (Figure 3A and Supplementary Table 1); 1847 of which were upregulated and 1533 of which were downregulated. In this comparison, as well as for Signature C, I had hypothesised an upregulation of *STAT1*, *STAT2* and *JAK2*, which are canonical IFNγ pathway genes, as well as *IRF1*, which is a key downstream signalling target of this cytokine (Majoros et al., 2017; Warre-Cornish et al., 2020). Indeed, *STAT1* (*FDR* = 5.572 x 10^{-6}; logFC = 5.680), *STAT2* (*FDR* = 5.045 x 10^{-6}; logFC = 2.247) and *IRF1* (*FDR* = 3.23 x 10^{-6}; logFC = 7.022) were among the top ten most significant DEGs for this signature, and *JAK2* was also significantly upregulated (*FDR* = 0.001; logFC = 2.111). The genes whose expression was most significantly altered by IFNγ treatment were *IFI27* (*FDR* = 2.97 x 10^{-6}; logFC = 6.067) and *CD274* (*FDR* = 2.97 x 10^{-6}; logFC = 6.386), both upregulated. Three genes encoding guanylate-binding proteins were among those that showed the highest fold change (logFC): *GBP1* (*FDR* = 3.11 x 10^{-5}; logFC = 14.622) *GBP5* (*FDR* = 0.0037; logFC = 13.473) and *GBP4* (*FDR* = 0.0002; logFC = 13.113) – also upregulated, as may be expected: guanylate-binding proteins (especially GBP1) are known to moderate the inflammatory activity of IFNγ (Honkala et al., 2019).

There were 168 pathways enriched in the comparison between IFNγ-treated cells and untreated cells in control lines; the gene set with the lowest *p*-value within the most significantly enriched cluster (Figure 3B) was 'immune system process' from Gene Ontology (*FDR* =0.0002; *NES* [Normalized Enrichment Score] = 2.41; gene sets in cluster = 1; genes in gene set = 1235), which consists of all genes involved in the development or functioning of the immune system. All of the top ten gene pathways for this signature were overexpressed amongst genes upregulated in response to IFNγ treatment. While most of these were related to the immune response initiated by cytokine exposure, there were, notably, two related to synaptic transmission: 'post-synaptic density, human core' and 'presynapse'.

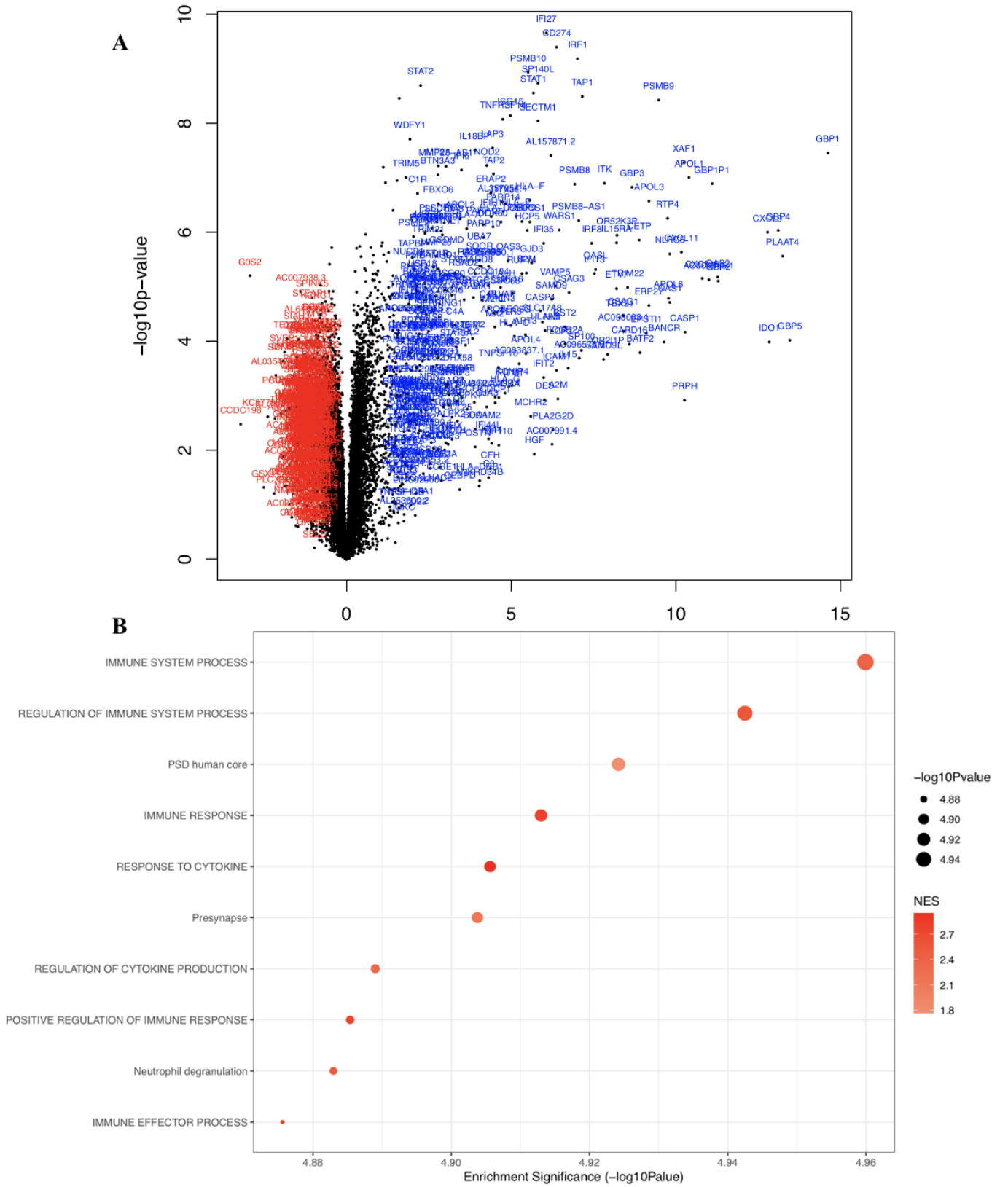


Figure 3. *Signature B.* **A.** The volcano plot shows, on the y-axis, the statistical significance (-log10 p-value) of differential expression of genes in IFNγ-treated control NPCs compared to untreated control NPCs. The x-axis is the magnitude of change ($\log_2$ fold change) in expression of those genes due to after IFNγ treatment. **B.** The top 10 significantly enriched gene set clusters (the gene set with the lowest *p*-value in each cluster is labelled on the y-axis). Please see Supplementary Spreadsheets 4A-G for full lists of enriched gene sets for each of the signatures. Data-points are sized according to significance ($-\log_{10}$ p-value) and coloured according to normalised enrichment score (NES), with blue indicating downregulation and red indicating upregulation.

Effect of IFNγ treatment in schizophrenia cell lines (Signature C)

There was also a significant effect of IFNγ treatment in schizophrenia cell lines at *FDR* < 0.05, with 1980 genes differentially expressed in IFNγ-treated schizophrenia cell lines compared to untreated schizophrenia lines (Figure 4A and Supplementary Table 2). Of these, 1061 were upregulated and 919 of which were downregulated. The genes whose expression was most significantly altered by IFNγ treatment in the schizophrenia neural progenitors were *STAT2* (*FDR* = 1.46 x 10^{-5}; logFC = 2.6103), *IFI27* (*FDR* = 1.74 x 10^{-5}; logFC = 6.331) and *STAT1* (*FDR* = 1.74 x 10^{-5}; logFC = 5.453). Once again, *IRF1* (*FDR* = 3.543 x 10^{-5}; logFC = 7.278) and *JAK2* (*FDR* = 0.0033; logFC = 1.846) were also significantly upregulated. Here too, the highest logFC was shown by *GBP1* (*FDR* = 3.91 x 10^{-5}; logFC = 12.308), followed by the pseudogene *GBP1P1* (*FDR* = 0.0001; logFC = 11.116).

There were 132 pathways enriched in the comparison of IFNγ-treated cells compared and untreated in schizophrenia lines; the gene set with the lowest *p*-value within the most significantly enriched cluster (Figure 4B) was, again, 'immune system process' (*FDR* =0.0002; *NES* = 2.366; gene sets in cluster = 1; genes in gene set = 1235). The results in this comparison show activation of similar pathways in response to IFNγ in schizophrenia lines as seen in control lines in the previous comparison (Figure 4B). However, the transcriptional response is attenuated, with fewer DEGs overall.

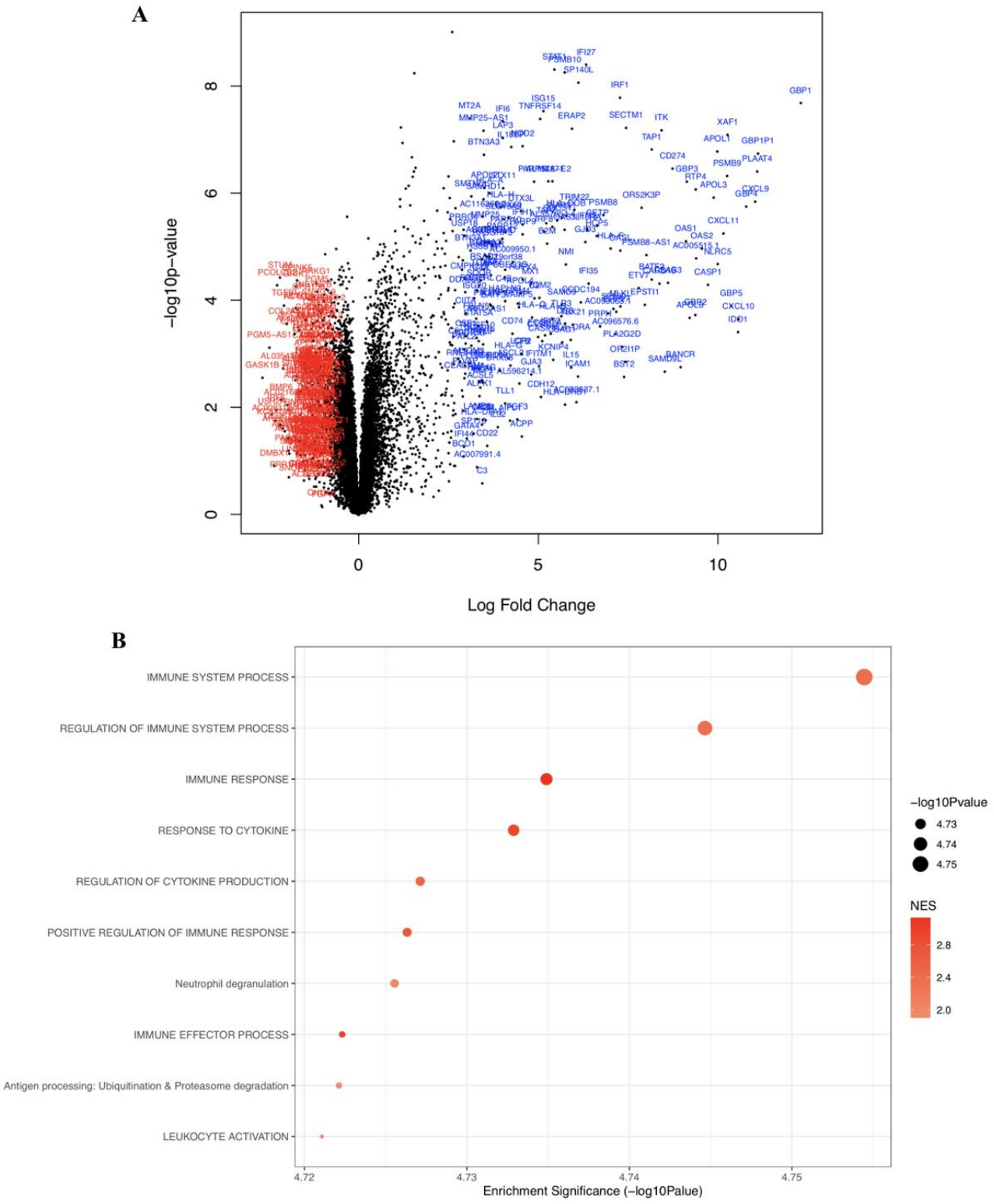


Figure 4. *Signature C.* **A.** The volcano plot shows, on the y-axis, the statistical significance (-$\log_{10}$ p-value) of differential expression of genes in IFNγ-treated schizophrenia (SCZ) NPCs compared to untreated SCZ NPCs. The x-axis is the magnitude of change ($\log_2$ fold change) in expression of those genes due to after IFNγ treatment. **B.** The top 10 significantly enriched gene set clusters (the gene set with the lowest *p*-value in each cluster is labelled on the y-axis). Please see Supplementary Spreadsheets 4A-G for full lists of enriched gene sets for each of the signatures. Data-points are sized according to significance (-$\log_{10}$ p-value) and coloured according to normalised enrichment score (NES), with blue indicating downregulation and red indicating upregulation.

Interaction effect of IFNγ treatment and schizophrenia diagnosis (Signature D)

To get a general picture of whether the patient lines respond differently to IFNγ treatment compared to how control lines do, I first examined the overlap of DEGs between signatures B and C (presented as a Venn diagram in Supplementary Figure 5). It was evident that of the 4137 genes that respond to IFNγ in any of the two groups, only 1223 genes are in common to both, meaning that there are 2914 genes that appear to respond differentially to IFNγ treatment between patients and controls. The following signature (Signature D) effectively assesses the same overlap; but subjects this comparison to an additional test of statistical significance. For this interaction term, multiple-testing correction was performed on the *p*-value obtained for the 4137 genes that are differentially expressed in response to IFNγ in any condition (controls and/or schizophrenia cells). At *FDR* < 0.05 there were 359 genes that respond significantly differently to IFNγ between control and schizophrenia cells (Figure 5A and Table 2); most significantly the mitochondrial complex genes *NDUFA2* (*FDR* = 0.0003; logFC = -0.591) and *NDUFS3* (*FDR* = 0.0006; logFC= -0.330), which were both downregulated. The highest fold change was exhibited by *AC092279.2* (*FDR* = 0.0006; logFC = 0.645).

There were twenty gene sets that were significantly overexpressed in this comparison, all amongst genes that are less expressed in response to IFNγ exposure by schizophrenia lines than by control lines (Figure 5B). The most significantly different of these were 'post-synaptic density (PSD), human core' (*FDR* =0.001; *NES* = -1.72; gene sets in cluster = 1; genes in gene set = 654), which includes several notable genes including the Alzheimer's risk gene *APOE*, autism and schizophrenia risk genes *NRXN1*, *CYFIP1* and *SHANK1-3*, NMDA receptor gene *GRIN1*, and *DLG4* which encodes the postsynaptic density protein PSD-95; as well as 'presynapse', which includes genes that regulate the pre-synaptic 'active zone' and synaptic vesicle formation (Pain et al., 2019; Pardiñas et al., 2018; Pocklington et al., 2015) – notable genes in this gene set include *SV2A* and *MAOA*. In other words, genes influencing synaptic transmission showed a particularly attenuated response to IFNγ treatment in schizophrenia lines.

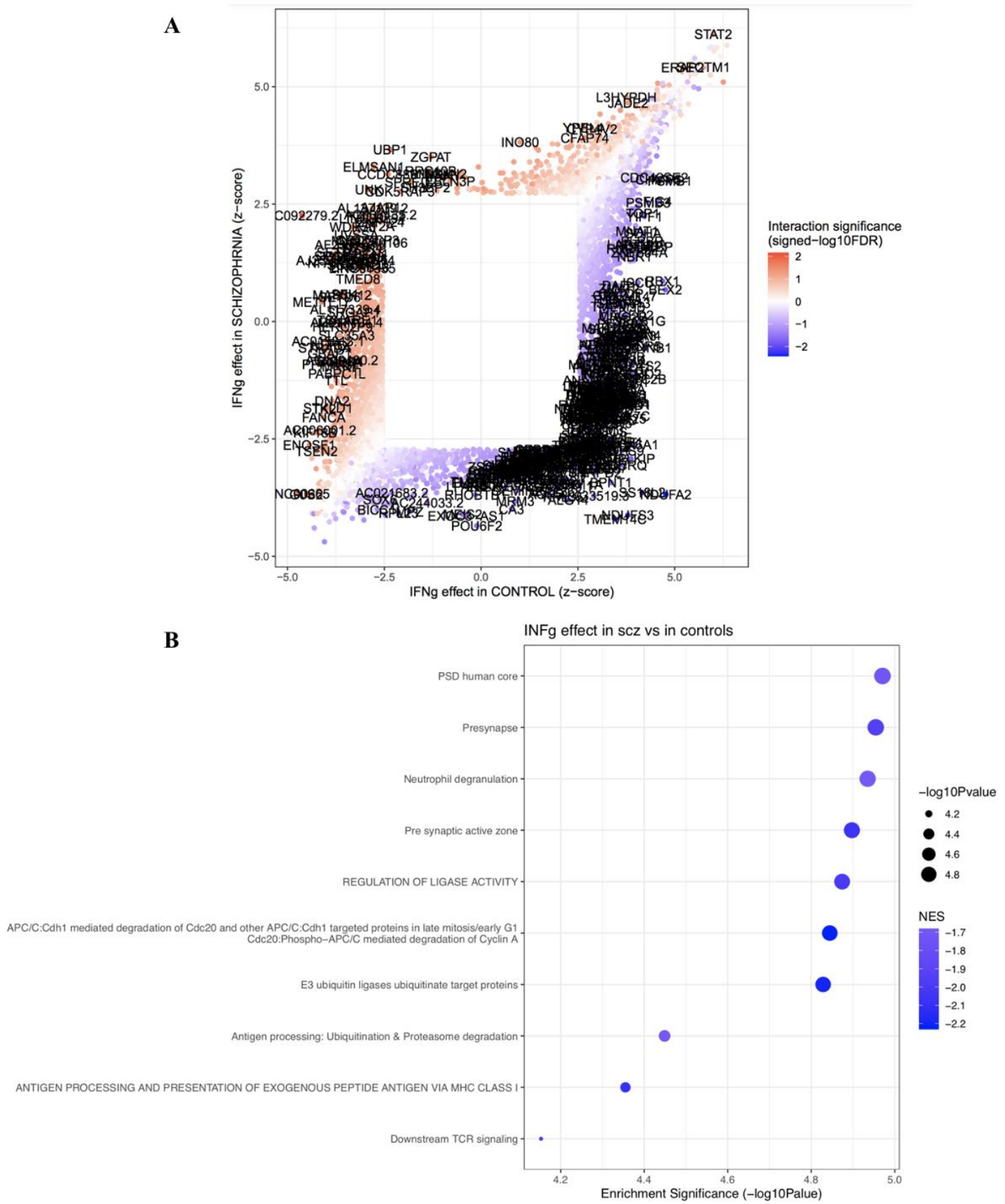


Figure 5. *Signature D.* **A.** The scatterplot shows IFNγ response results for Signature D (i.e., the interaction effect between IFNγ-treatment and diagnostic group on gene expression) in the 4137 genes that responded differentially to IFNγ in Signatures B and C. DEGs for control cells are on the *x*-axis and DEGs for schizophrenia cells are on the *y*-axis. The data are coloured by signed -$\log_{10}$FDR obtained for the interaction term (with blue indicating downregulation and red indicating upregulation). The 359 significant genes that are significant in the interaction are labelled. **B.** The top ten significantly enriched gene set clusters (the gene set with the lowest *p*-value in each cluster is labelled on the y-axis). Data-points are sized according to significance (-$\log_{10}$ p-value) and coloured according to normalised enrichment score (NES), with darker blue indicating greater downregulation.

Table 2. Top 20 genes significantly differentially expressed in IFNγ-treated compared to untreated cell lines in schizophrenia versus controls (Signature D) – all of these are downregulated. The right side of the table shows the effect of IFNγ treatment on the same genes in controls only, for comparison. Please see Supplementary Spreadsheet 3D for differential expression results for all genes in this comparison. A negative logFC indicates downregulation.

Gene Symbol	IFN-γ effect in schizophrenia versus in controls				IFN-γ effect in controls			
	Log Fold Change	Average[2] Expression	*p*-value	FDR[1]	Log Fold Change	Average Expression	*p*-value[3]	FDR[1]
NDUFA2	-0.591	4.976	1.00E-06	3.27E-04	0.405	4.976	0.000	0.000
NDUFS3	-0.330	6.229	5.00E-06	5.84E-04	0.145	6.229	0.000	0.005
SS18L2	-0.587	4.809	6.00E-06	5.84E-04	0.153	6.628	0.001	0.009
TMEM14C	-0.411	6.628	7.00E-06	5.84E-04	0.342	4.809	0.000	0.002
AC092279.2	0.645	3.906	9.00E-06	6.19E-04	-0.517	3.906	0.000	0.001
BEX2	-0.291	5.997	2.30E-05	1.38E-03	0.307	5.997	0.000	0.000
RBX1	-0.414	6.291	3.20E-05	1.64E-03	0.445	6.291	0.000	0.000
MPLKIP	-0.506	5.272	4.30E-05	1.93E-03	0.322	5.272	0.000	0.004
COX6A1	-0.605	5.983	4.90E-05	1.95E-03	0.418	5.983	0.000	0.003
UQCRQ	-0.669	5.772	5.50E-05	1.96E-03	0.392	5.772	0.000	0.006
AL033519.3	-1.604	0.605	6.90E-05	2.26E-03	0.651	0.605	0.004	0.026
ALG14	-0.597	3.048	1.29E-04	2.26E-03	0.176	3.048	0.024	0.082
ATP5F1E	-0.714	7.683	2.50E-04	2.26E-03	0.430	7.683	0.001	0.012
BPNT1	-0.661	4.865	8.50E-05	2.26E-03	0.307	4.865	0.001	0.012
BTF3	-0.371	8.866	1.91E-04	2.26E-03	0.168	8.866	0.003	0.025
CA3	-0.936	1.623	2.51E-04	2.26E-03	0.089	1.623	0.432	0.574
CHCHD2	-0.430	6.979	1.60E-04	2.26E-03	0.378	6.979	0.000	0.003
COA3	-0.507	5.485	2.22E-04	2.26E-03	0.490	5.485	0.000	0.002
COPS9	-0.804	5.617	9.30E-05	2.26E-03	0.512	5.617	0.000	0.007
COX7C	-0.552	7.975	1.50E-04	2.26E-03	0.409	7.975	0.000	0.005

[1] False Discovery Rate
[2] Expression of the gene in (TMM-normalized) $\log_2$ CPMs (counts-per-million) averaged across all samples
[3] Uncorrected *p*-values

Table 3. Top 20 gene sets significantly overrepresented among DEGs in IFNγ-treated compared to untreated cell lines in schizophrenia versus controls (Signature D). The right side of the table shows the effect of IFNγ treatment on the same genes in controls only, for comparison. Please see Supplementary Spreadsheet 4D for differential expression results for all genes in this comparison.

Gene Set	IFN-γ effect in schizophrenia versus in controls					IFN-γ effect in controls		
	Database	*p*-value	ES[1]	NES[2]	Number of genes in set	*p*-value	ES[1]	NES[2]
PSD human core	OP	1.07E-05	-0.32686	-1.719	654	1.19E-05	0.297	1.764
Presynapse	OP	1.11E-05	-0.37736	-1.944	465	1.25E-05	0.369	2.136
Synaptic vesicle	OP	1.15E-05	-0.35428	-1.787	353	1.30E-05	0.360	2.028
Neutrophil degranulation	Reactome	1.16E-05	-0.33523	-1.681	330	1.31E-05	0.444	2.483
Presynaptic active zone	OP	1.27E-05	-0.44027	-2.068	177	1.43E-05	0.402	2.085
Regulation of ligase activity	GO	1.34E-05	-0.44658	-1.994	121	1.53E-05	0.505	2.402
Positive regulation of ligase activity	GO	1.37E-05	-0.47269	-2.056	102	1.53E-05	0.505	2.402
Cdc20:Phospho-APC/C mediated degradation of Cyclin A	Reactome	1.43E-05	-0.54536	-2.224	70	1.58E-05	0.599	2.661
APC/C:Cdh1 mediated degradation of Cdc20 and other APC/C:Cdh1 targeted proteins in late mitosis/early G1	Reactome	1.43E-05	-0.54725	-2.232	70	1.58E-05	0.601	2.668
APC/C:Cdc20 mediated degradation of Securin	Reactome	1.44E-05	-0.57565	-2.316	65	1.60E-05	0.642	2.806
Activation of NF-kappa-B in B cells	Reactome	1.44E-05	-0.53276	-2.137	64	1.60E-05	0.648	2.826
Autodegradation of Cdh1 by Cdh1:APC/C	Reactome	1.45E-05	-0.57029	-2.281	63	1.60E-05	0.650	2.825
E3 ubiquitin ligases ubiquitinate target proteins	Reactome	1.48E-05	-0.57381	-2.195	50	1.64E-05	0.549	2.273
Hedgehog ligand biogenesis	Reactome	2.93E-05	-0.55385	-2.166	56	1.62E-05	0.684	2.900
Cross-presentation of soluble exogenous antigens (endosomes)	Reactome	3.01E-05	-0.58254	-2.170	44	1.65E-05	0.748	3.007
Antigen processing: Ubiquitination & Proteasome degradation	Reactome	3.56E-05	-0.34313	-1.697	283	1.34E-05	0.448	2.466
Antigen processing and presentation of exogenous peptide antigen via MHC1	GO	4.42E-05	-0.53871	-2.093	54	1.43E-05	0.549	2.833
Downstream TCR signalling	Reactome	7.04E-05	-0.4687	-1.958	80	1.57E-05	0.634	2.889
Ligand gated channel activity	GO	7.05E-05	0.40826	1.952	85	2.80E-05	-0.482	-2.412
Reactive oxygen species pathway	Hallmark	7.51E-05	-0.5478	-2.050	45	1.65E-05	0.579	2.338

[1]Enrichment Score
[2]Normalised Enrichment Score

Effect of IL-1β treatment on gene expression (Signature E, F & G)

I had expected to see an upregulation of the IL-1β pathway genes, *MYD88* and *IRAK4*, as well as the downstream signalling target *NFKB* (Weber et al., 2010) but here was no significant effect of IL-1β treatment in either control (Figure 6A) or schizophrenia (Figure 7A) lines. Nevertheless, there were 123 and 112 pathways enriched for signatures E and F, respectively. For signature E, 'regulation of immune system process' was most significant (*FDR* =0.0005; *NES* = 1.55; gene sets in cluster = 3; genes in gene set = 888); and 'Lek2015 loss-of-function (90)' (Pain et al., 2019; Pardiñas et al., 2018; Pocklington et al., 2015) was most significant for signature F (*FDR* =0.0008; *NES* = -1.97; gene sets in cluster = 1; genes in gene set = 3007). The interaction effect between IL-1β and schizophrenia diagnosis (Signature G) also did not yield any significantly differentially expressed genes (Figure 8A) but did yield 15 gene sets that were significantly enriched – the top nine amongst genes less expressed in schizophrenia NPCs response to IL-1β (Figure 8B), with 'regulation of ligase activity' having the lowest *p*-value of the most significant cluster for signature G (*FDR* =0.0015; *NES* = -2.15; gene sets in cluster = 2; genes in gene set = 121). The fact that there are significant gene set enrichment terms for this comparison despite there being no DEGs suggests that there are indeed some effects of IL-1β on transcription, but the sample is underpowered to detect them individually. Pathway enrichment compresses the number of tests (here, there are 15061 genes but only 895 gene sets), making it more likely to identify these effects. The enrichment results here also show a suppression of transcriptional response to IL-1β exposure in schizophrenia NPCs, with pathways regulating the post-synaptic density and presynapse once again amongst the top ten (Figure 8B).

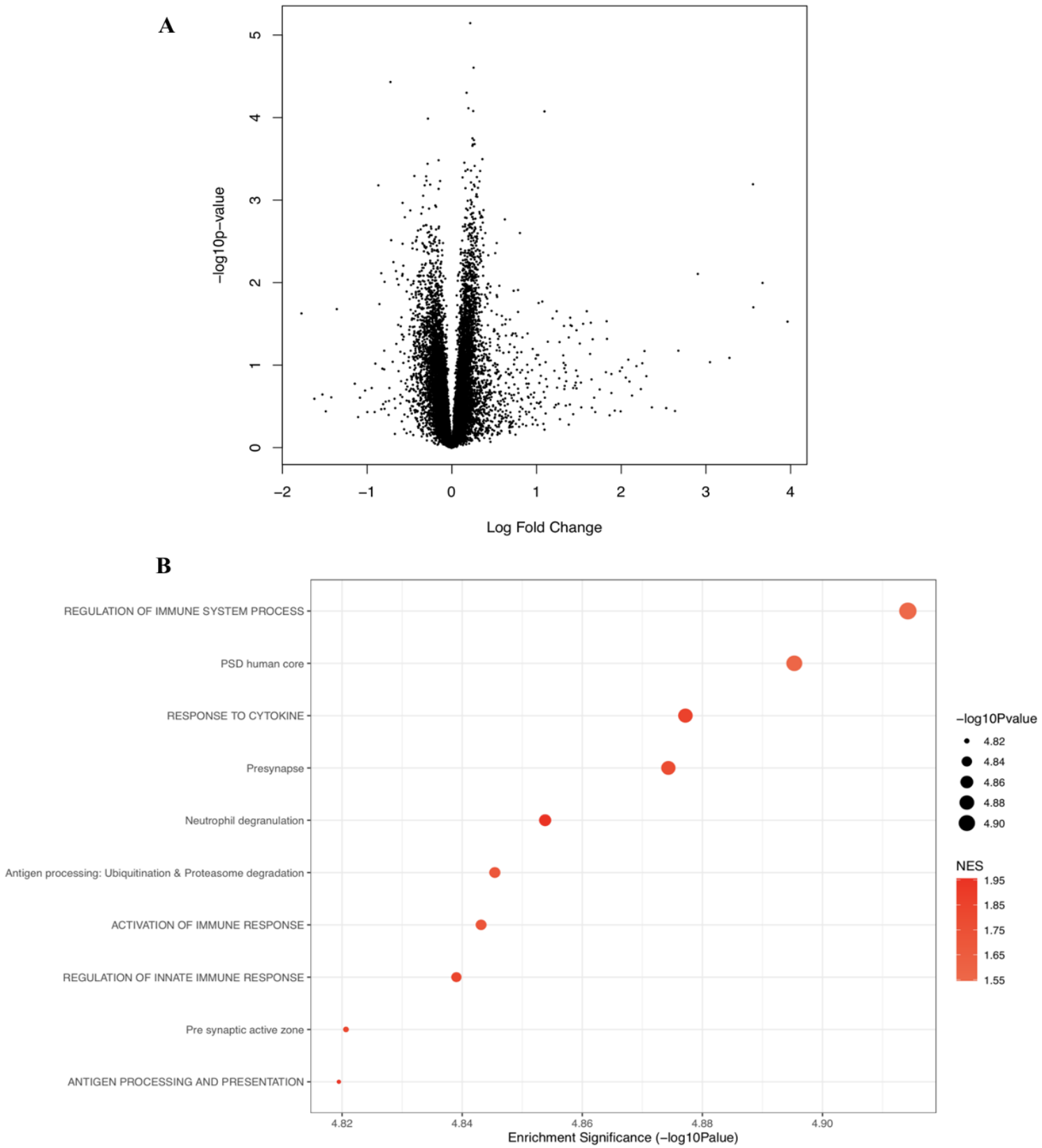


Figure 6. *Signature E.* **A.** The volcano plot shows, on the *y*-axis, the statistical significance (-$\log_{10}$ p-value) of differential expression of genes in IL-1β-treated compared to untreated control cells. The *x*-axis is the magnitude of change ($\log_2$ fold change) in expression of those genes after IL-1β treatment. **B.** The top 10 significantly enriched gene set clusters (the gene set with the lowest *p*-value in each cluster is labelled on the *y*-axis). Data-points are sized here according to significance (-$\log_{10}$ p-value), and coloured according to the normalised enrichment score (NES), with darker red indicating greater upregulation.

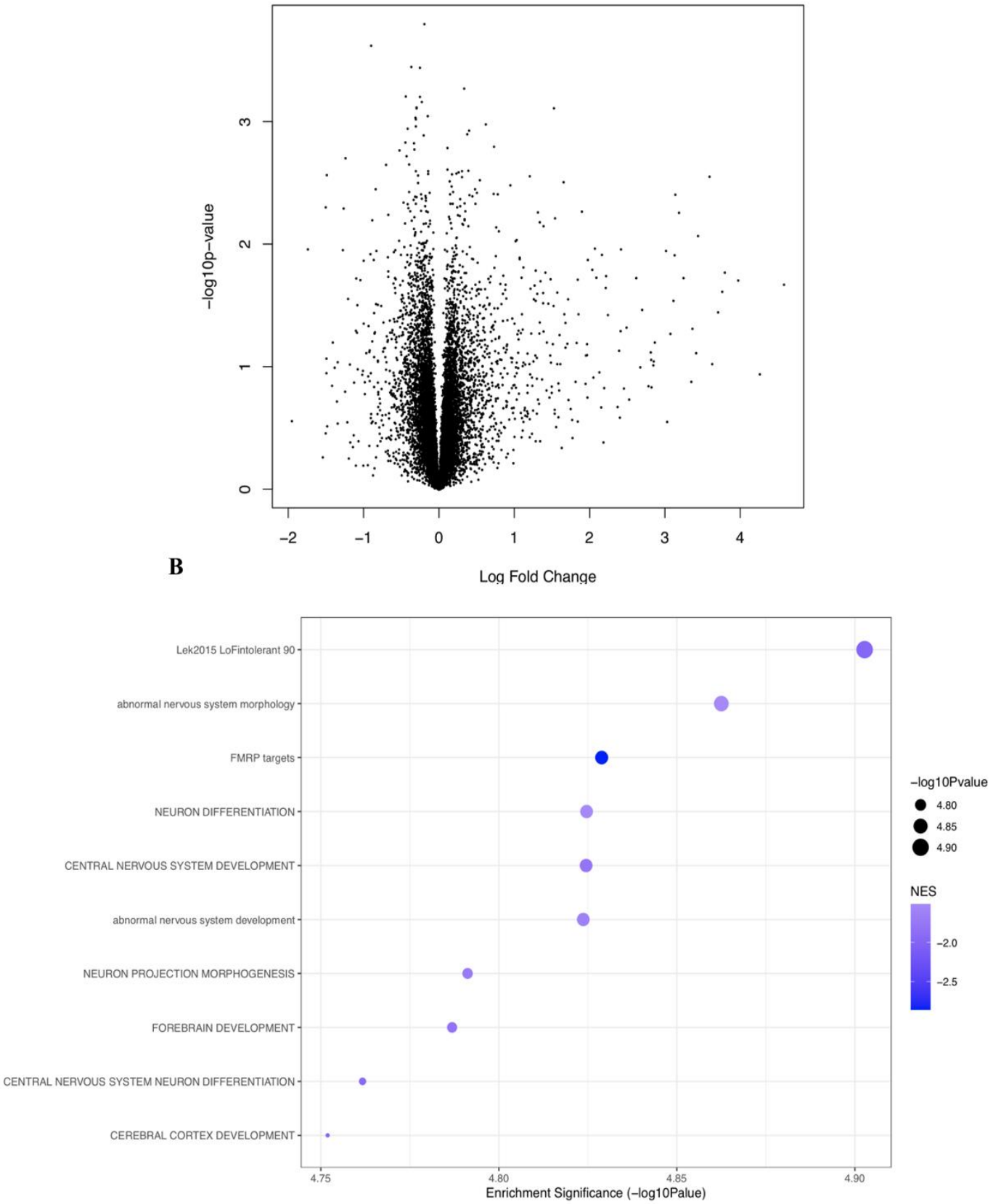


Figure 7. *Signature F.* **A.** The volcano plot shows, on the *y*-axis, the statistical significance (-$\log_{10}$ p-value) of differential expression of genes in IL-1β-treated compared to untreated cells from patient (SCZ) donors. The *x*-axis is the magnitude of change ($\log_2$ fold change) in expression of those genes after IL-1β treatment. **B.** The top 10 significantly enriched gene set clusters (the gene set with the lowest *p*-value in each cluster is labelled on the *y*-axis). Data-points are sized according to significance (-$\log_{10}$ p-value) and coloured according to normalised enrichment score (NES), with darker blue indicating greater downregulation.

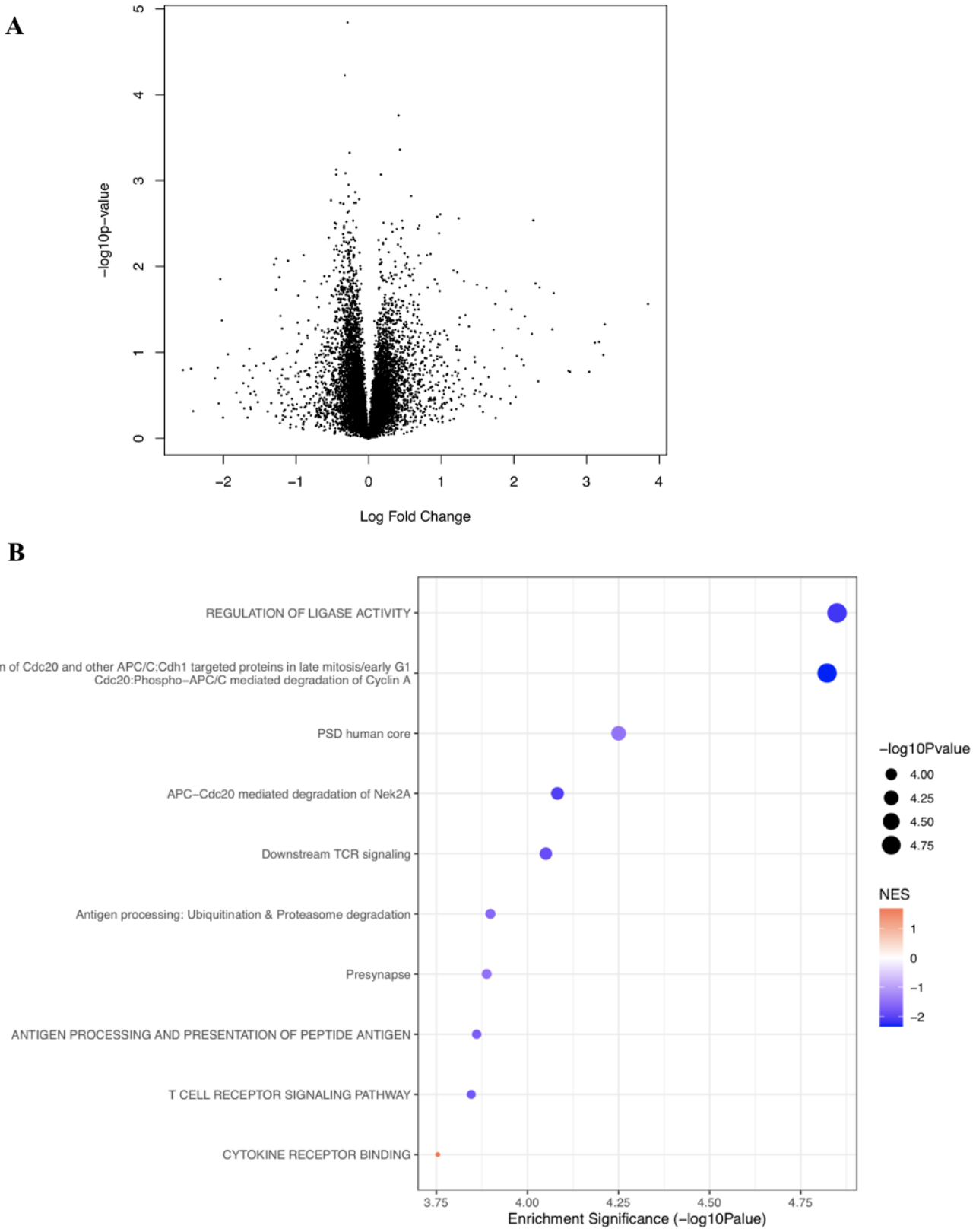


Figure 8. *Signature G.* **A.** The volcano plot shows, on the *y*-axis, the statistical significance (-$\log_{10}$ p-value) of differential expression of genes in IL-1β-treated compared to untreated cells from patient donors versus those from control donors (i.e., the interaction effect between IL-1β -treatment and diagnostic group on gene expression). The *x*-axis is the magnitude of change ($\log_2$ fold change) in expression of those genes after IL-1β treatment. **B.** The top ten significantly enriched gene set clusters (the gene set with the lowest *p*-value in each cluster is labelled on the *x*-axis). Data-points are sized according to significance (-$\log_{10}$ p-value) and coloured according to normalised enrichment score (NES), with blue indicating downregulation and red indicating upregulation.

Differential expression of receptor genes

To assess whether the transcriptional responses to IL-1β and IFNγ were influenced by the expression of their respective receptors in the NPC cultures, I compared the expression of *IL1R1, IL1R2, IL1RAP, IFNGR1 and IFNGR2* between patient and control lines. IL-1β receptor genes exhibit visibly lower expression than the IFNγ receptors (Figure 10) in all the cell lines, which may explain the low responsiveness of the neural progenitors to IL-1β stimulation. In the schizophrenia cell lines, there was a lower expression of *IFNGR2* compared to controls (Figure 11), which may explain there being fewer DEGs in response to IFNγ stimulation in schizophrenia NPCs.

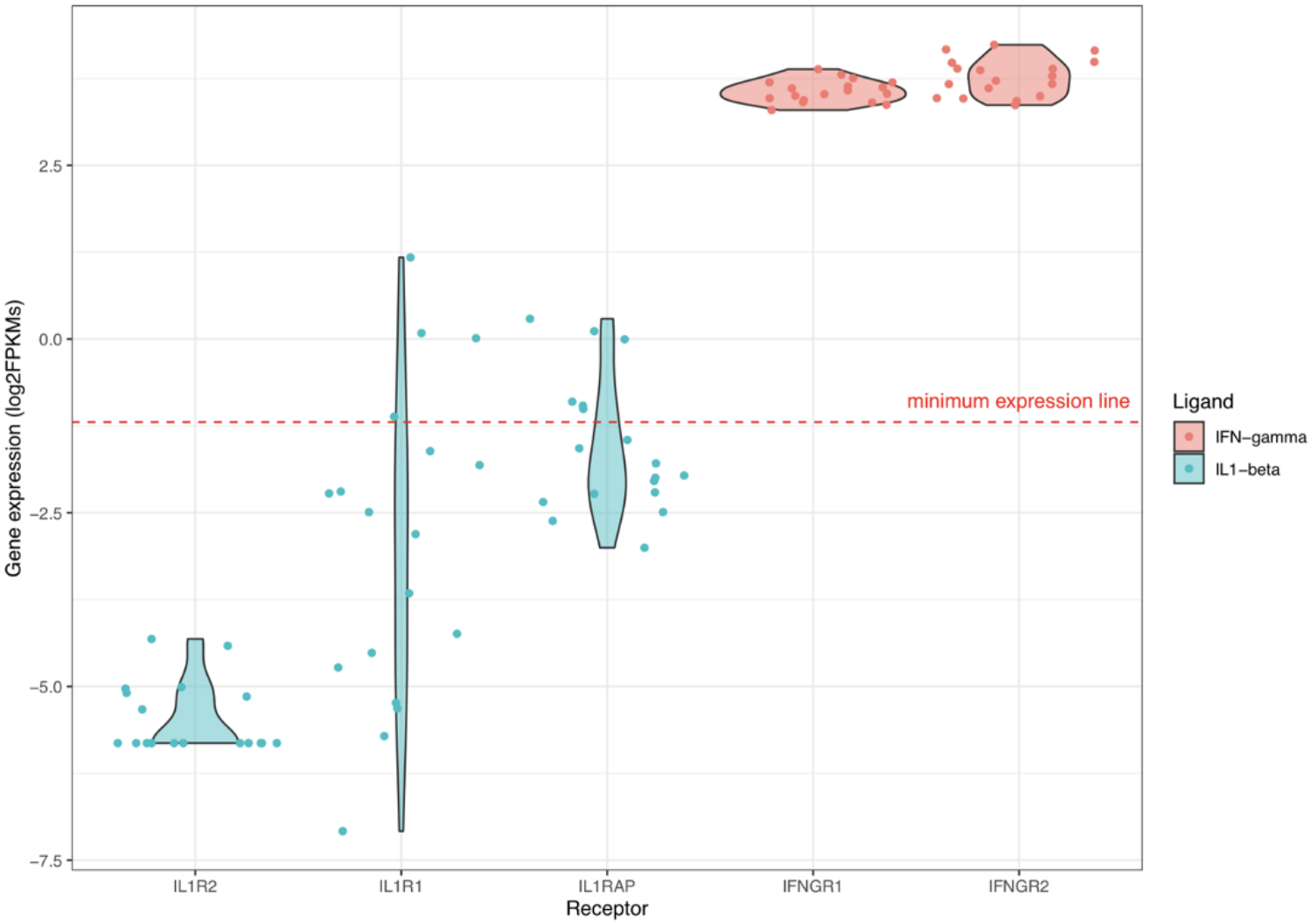


Figure 10. *Distribution of cytokine receptor expression across all samples.* The violin plot shows the distribution of the expression (in FPKMs) of each of the five receptor genes [Interleukin 1 Receptor 2 (*IL1R2*); Interleukin 1 Receptor 1 (*IL1R1*); Interleukin 1 Receptor Accessory Protein (*IL1RAP*); Interferon Gamma Receptor 1 (*IFNGR1*); and Interferon Gamma receptor 2 (*IFNGR2*)], across all samples, normalised by gene length and library size.

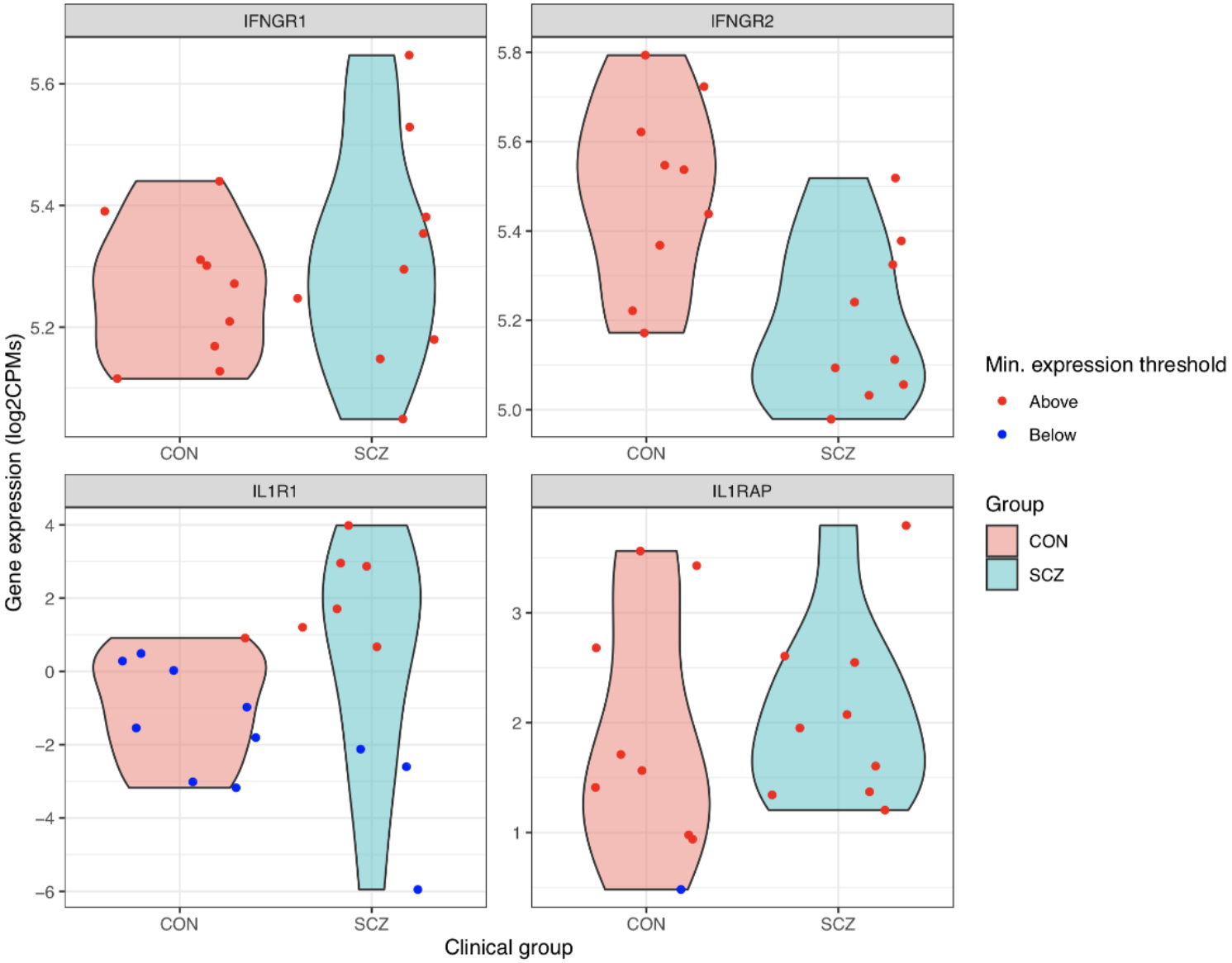


Figure 11. Expression of cytokine receptors in schizophrenia cell lines compared to controls. Shows the differential gene expression in schizophrenia (SCZ) compared to controls (CON) the four cytokine receptor genes that passed low-expression filtering. Values that lie above minimum expression threshold (log_2 CPM = 0.6) are shown in red.

Discussion

In this study, I sought to assess how the cytokines interferon-gamma (IFNγ) and interleukin-1 beta (IL-1β) interact with genetic profiles associated with schizophrenia in order to better understand the increased susceptibility to schizophrenia seen in offspring of mothers exposed to infection during pregnancy. I hypothesised that cortical neural progenitor cells (NPCs) derived from patients with schizophrenia would respond differently to IFNγ or IL-1β exposure compared to those of healthy controls. To my knowledge, this is the first study to assess the influence of these cytokines on gene expression in NPCs from patients with schizophrenia; and the second, after (Warre-Cornish et al., 2020), to administer transient immune stimulation to human neural progenitors.

There was only one gene that was significantly differentially expressed in schizophrenia lines compared to controls in the absence of treatment. At face value, this is surprising, as previous research (Evgrafov et al., 2020) has shown at least eighty DEGs for schizophrenia. However, it may be that the effects of many of these genes individually are weak, and the relatively small sample is underpowered to detect them. (Indeed, Evgrafov et al. (2020) had a much larger sample size than the one in the current study and used a more lenient multiple testing correction threshold, *FDR* < 10%). If this is the case, one would expect some of these effects to be captured in gene set enrichment analyses. I did indeed see enrichment of 26 sets of genes, particularly those sensitive to loss-of-function mutations, pointing to a potential genomic instability of schizophrenia lines. There was also enrichment of genes related to antigen presentation in schizophrenia lines compared to controls; particularly those related to major histocompatibility complex class I (MHC-I), which presents antigens on cell surfaces for detection by T-cells and has a well-established relationship with schizophrenia (Psychosis Endophenotypes International Consortium et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Shi et al., 2009).

I then assessed whether IFNγ treatment alters transcriptional responses in control neural progenitors and found that there were 3380 genes significantly differentially expressed in response to

IFNγ treatment. This is interesting itself, as the cell cultures used in this study do not contain glial cells – supporting the notion presented by Warre-Cornish et al. (2020) that NPCs can launch an immune response independent of microglia. Immune responses in the brain are thought to be predominantly mediated by glia (Greenhalgh et al., 2020), but the fact that neural progenitor cells are themselves responsive to a proliferation of IFNγ (which initiates an immune response to viral infection) indicates that immunity in the brain extends beyond glial cells. Moreover, in both control and schizophrenia neural progenitor cell lines, IFNγ treatment activated the canonical *JAK-STAT* signalling pathway, as would typically be seen in response to viral infection. The findings for this comparison were also consistent with recent work which found MHC-I related genes among the most differentially expressed in IFNγ-treated control neural progenitors and neurons (Warre-Cornish et al., 2020). In my results (Supplementary Spreadsheet 3A), key MHC-I related genes such as *HLA-A, HLA-B* and *HLA-C* are all consistently upregulated in response to IFNγ treatment. However, in the current study, the genes most significantly upregulated on IFNγ exposure were *IFI27* and *CD274*. *IFI27* encodes Interferon Alpha Inducible Protein 27, which is involved in interferon-induced apoptosis and is considered to be a biomarker that differentiates between viral and bacterial infection (Tang et al., 2017). *CD274* encodes a receptor ligand that binds to PD-1 receptors on T-cell surfaces, inhibiting T-cell activation and antibody production – an essential process for preventing autoimmunity (Francisco et al., 2010).

In schizophrenia cell lines, there were far fewer differentially expressed genes in response to IFNγ treatment: only 1980. This may be, in part, due to the lower expression of the IFNγ receptor gene *IFNGR2* in schizophrenia cell lines compared to control lines. It could also be that these cells are not able to activate in response to IFNγ to the same extent as controls. The top ten most significant IFNγ-responding genes in schizophrenia lines were almost exactly the same as those in control lines; although, interestingly, I saw completely opposite DGE responses to IFNγ treatment in control cell lines compared to schizophrenia cell lines (Table 2). Physiologically, this may mean that cells from healthy donors

exhibit a compensatory transcriptional response to infection which does not occur in cells from donors with schizophrenia, resulting in a greater insult to neurodevelopment in the latter. The top two of these DEGs (*NDUFA2* and *NDUFS3*) being mitochondrial complex I genes suggests that schizophrenia donor cells may be driven to conserve energy in response to an infection, while healthy donor cells are able to expend more energy to restore health (Mueller et al., 2021) (Park 2020; Mueller, 2021).

The same gene, *GBP1*, also showed the highest fold change in response to IFNγ in both groups, which is to be expected as *GBP1* encodes an interferon-induced guanylate-binding protein that is also part of the canonical IFNγ signalling pathway. The lower number of IFNγ-induced differentially expressed genes in schizophrenia lines also points to a gene-environment interaction: the genetic profiles of patients with schizophrenia may characteristically influence the way in which their brains respond to these cytokines. Indeed, 359 (of 4137 that respond differentially to IFNγ in any of the lines) genes responded significantly differently to IFNγ exposure when the differential expression of schizophrenia and control cell lines were compared. Of these, the two most significant, *NDUFA2* and *NDUFS3* encode subunits of the NADH:Ubiquinone Oxidoreductase complex, which is involved in the energy-regulating mitochondrial electron transport chain, supporting previous observations of mitochondrial dysfunction in schizophrenia and other psychiatric disorders (Rajasekaran et al., 2015). This is also congruous with a recent study which found a downregulation of *NDUFA2* in mice susceptible to the behavioural consequences of immune activation by poly(I:C) (Mueller et al., 2021). Interestingly, these genes are also part of the endocannabinoid signalling pathway (KEGG), as CB1 cannabinoid receptors are expressed both at presynaptic terminals and in mitochondrial membranes. Synaptic CB1 receptors can, when activated, inhibit the release of neurotransmitters GABA (γ-amino butyric acid) and glutamate and are themselves strongly implicated in schizophrenia (D'Souza et al., 2005; Guennewig et al., 2018; Shum et al., 2020).

The gene sets significantly enriched for IFNγ treatment in both schizophrenia and control lines largely converged in function, as expected, upon immune regulation. The gene sets that responded most differently to IFNγ in schizophrenia lines were those regulating the postsynaptic density, presynapse, and presynaptic active zone. This result sits well with models of schizophrenia from other fields of neuroscience, including the concept of schizophrenia as a disorder of synaptic 'dysconnection' in computational neuroscience – a promising bridge between two very different but equally rich views of the same disorder. The dysconnection hypothesis suggests a dysregulation of neuromodulation (particularly across glutamatergic synapses) lies at the core of the various factors contributing to susceptibility (R. A. Adams et al., 2013; Friston et al., 2016). An important inference here is that any structural deficits of connectivity seen in schizophrenia are caused by aberrant synaptic transmission, presumably as synapses that miscommunicate are more likely to be pruned away (Friston et al., 2016; Stephan et al., 2006; Stephan et al., 2009). This is consistent with cortical neuropathology in schizophrenia on a cellular level, where numbers of dendrites (Gilmore et al., 2004), spines and synaptic proteins (Friston et al., 2016; Glantz & Lewis, 1997), but not of neurons, are significantly reduced. The results of the current study appear to support this theory.

It is very likely the absence of DEGs in response to IL-1β treatment in any of the lines is related to the low expression of IL1 receptor 1 (*IL1R1*) across all the cell lines: blocking the IL1R1 significantly reduces the influence of IL-1β on neural progenitors (Crampton et al., 2012). However, this low IL-1 receptor expression was surprising in light of previous work showing high *IL1R1* (but not *IL1R2*) expression in rat ventral mesencephalon neural progenitors (Crampton et al., 2012). It is possible that there is lower *IL1R1* expression in the cortex than in other parts of the foetal brain; or perhaps *IL1R1* expression is upregulated at a later stage of prenatal neurodevelopment in humans than in rats, which would demonstrate the significance of leveraging human systems in the study of human

neurodevelopment. It is also possible that that, by the 24-hour time point, any effect induced by IL-1β may have been lost – i.e., the effects of IL-1β may be very rapid and transient.

Nevertheless, pathway analyses did reveal significant enrichment of gene sets in response to IL-1β treatment, likely due to the reduced number of tests (895 rather than 15061) allowing more subtle effects to come to the fore. This analysis showed very different response profiles in patient neural progenitors compared to control neural progenitors. Among the top ten most significantly enriched gene sets in control lines treated with IL-1β were (as with IFNγ) genes regulating the immune response, the presynapse and the post-synaptic density – all upregulated. However, none of these top ten gene sets were among those most significantly enriched in IL-1β-treated schizophrenia lines; instead, almost all of these were sets of genes involved in central nervous system development and neuronal morphogenesis – all downregulated. Among the gene sets that responded significantly differently to IL-1β in schizophrenia lines compared to controls were those involved in cell division, antigen presentation and, once again, synaptic transmission.

There are, of course, limitations to the current study; most of all, the relatively small sample size, which would warrant future replication studies. The sample was also fairly heterogeneous in terms of genetic background, which meant individual differences considerably influenced genetic variance in the sample. In particular, there were differences in polygenic risk score (PRS) for schizophrenia that could confound or further limit power to identify case-control differences. Specifically, one of the cases included had a high PRS with a sparse history of cannabis use, while another had a low PRS with a frequent history of cannabis use (PRS was not available for the other lines). In theory, one would expect that reprogramming the keratinocyte samples into iPSCs would negate epigenetic effects such as those related to cannabis use. For the same reason, it was also surprising to find that donor age had some influence over the genetic variance in the sample, as one would also expect a negation of age-related epigenetic effects. It is likely that this is due to noise (again as a result of the small sample size), which

emphasises the importance of replicating these findings. Finally, I administered a single, acute dose of cytokine treatment to my NPC cultures: in future studies, it would be interesting to examine the effect of chronic treatment.

In summary, I have found that immune activation induced by IL-1β and IFNγ elicits transcriptional changes that may alter the course of subsequent neurodevelopment. These findings exemplify differences in how the brains of people with schizophrenia may have responded to infection or inflammation during prenatal development. This in turn suggests that immune insults early in life may alter neurotransmission. Finally, I identify new gene targets for future research on the influence of maternal immune activation on schizophrenia susceptibility and resilience.

Supplementary Information

Supplementary Table 1. Top 20 genes most significantly differentially expressed in IFNγ-treated control cells compared to untreated control cells.

Gene Symbol	Log fold change	Average expression[2]	P value	Adjusted P value	Z score	FDR[1]
IFI27	6.067	4.280	2.16E-10	2.97E-06	6.350	2.97E-06
CD274	6.386	1.547	3.95E-10	2.97E-06	6.256	2.97E-06
IRF1	7.022	4.265	6.44E-10	3.24E-06	6.179	3.23E-06
PSMB10	5.522	1.528	1.15E-09	4.32E-06	6.087	4.33E-06
SP140L	5.815	0.465	1.81E-09	5.05E-06	6.014	5.05E-06
STAT2	2.247	6.869	2.01E-09	5.05E-06	5.997	5.05E-06
STAT1	5.680	7.882	2.74E-09	5.58E-06	5.946	5.57E-06
TAP1	7.167	4.928	3.18E-09	5.58E-06	5.922	5.57E-06
GSTK1	1.608	5.890	3.47E-09	5.58E-06	5.908	5.57E-06
PSMB9	9.482	2.362	3.70E-09	5.58E-06	5.897	5.57E-06
ISG15	4.980	4.931	7.22E-09	9.89E-06	5.786	9.88E-06
TNFRSF14	4.751	1.658	8.30E-09	1.04E-05	5.762	1.04E-05
SECTM1	5.813	0.609	9.07E-09	1.05E-05	5.747	1.05E-05
WDFY1	1.922	7.012	1.94E-08	2.09E-05	5.617	2.09E-05
LAP3	4.433	6.512	2.85E-08	2.86E-05	5.551	2.86E-05
IL18BP	3.892	4.188	3.13E-08	2.95E-05	5.534	2.95E-05
GBP1	14.622	2.693	3.51E-08	3.11E-05	5.514	3.11E-05
AL157871.2	6.200	-0.603	3.88E-08	3.25E-05	5.496	3.25E-05
XAF1	10.252	-1.583	5.23E-08	4.15E-05	5.443	4.15E-05

[1] False Discovery Rate

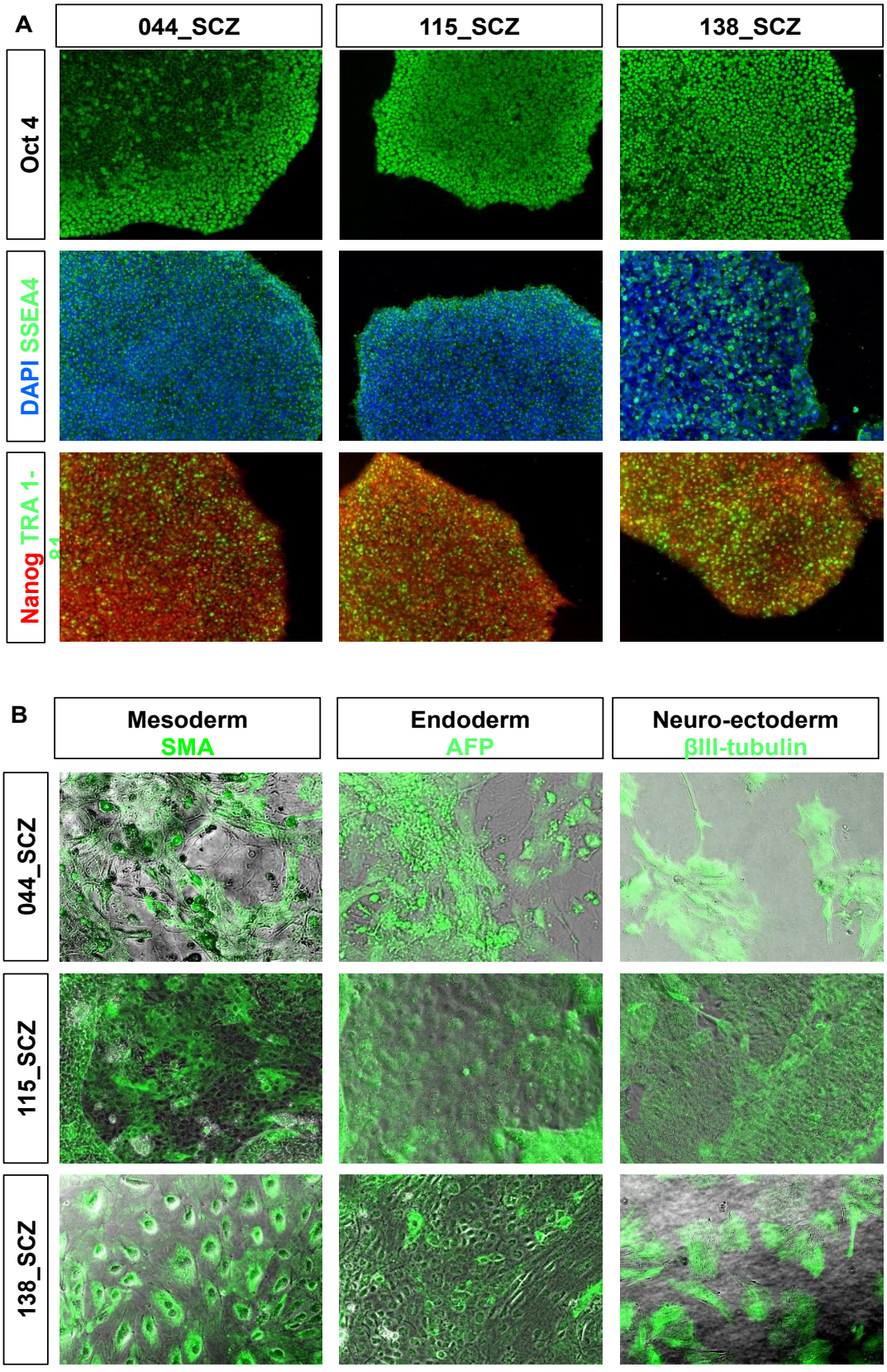
[2] Average expression of the gene in TMM-normalised $\log_2$ CPMs (counts-per-million).

Supplementary Table 2. Top 20 genes most significantly differentially expressed in IFNγ-treated schizophrenia cell lines compared to untreated schizophrenia cell lines.

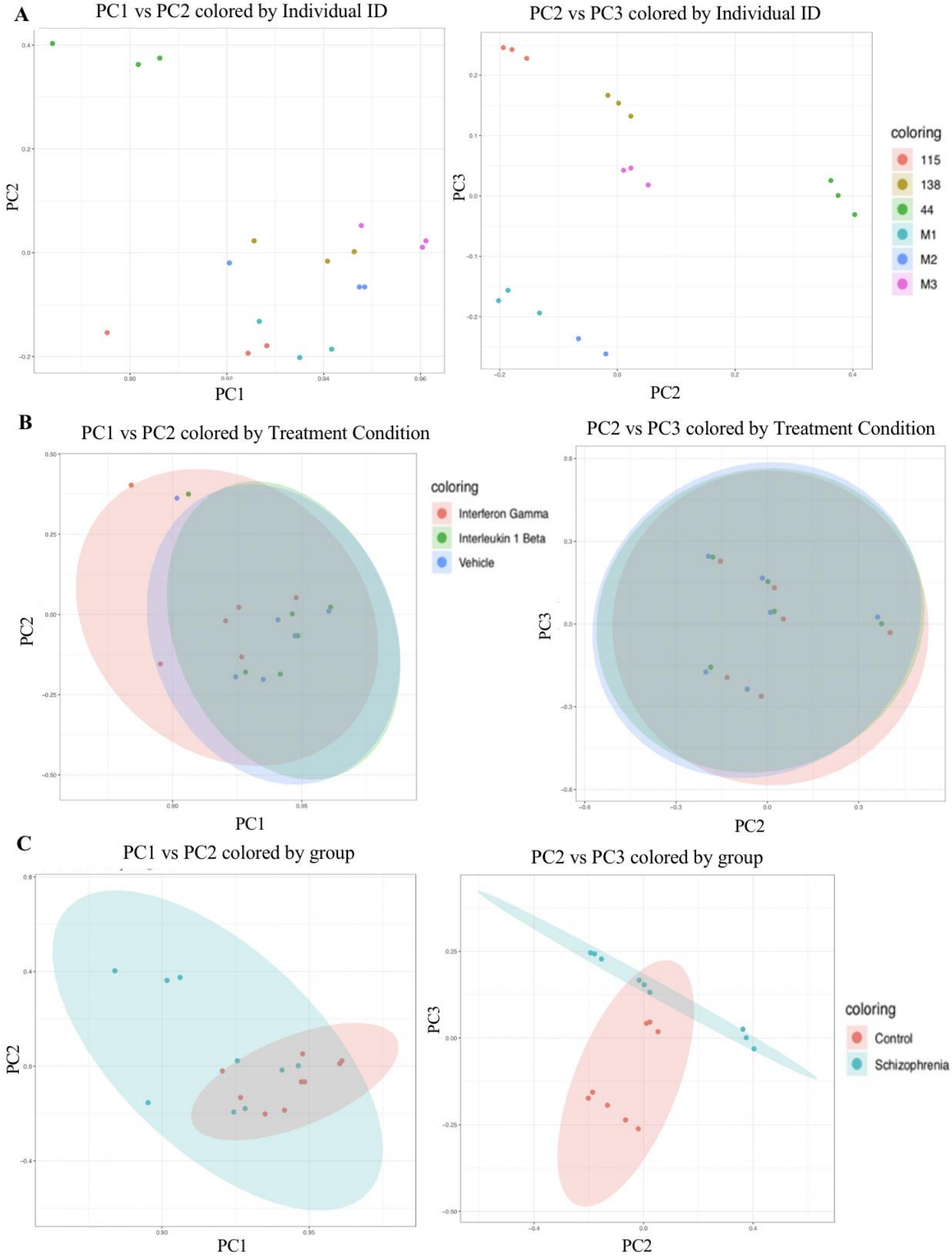
Gene Symbol	Log fold change	Average expression[2]	P value	Adjusted P value	Z score	FDR[1]
STAT2	2.610	6.869	9.67E-10	1.46E-05	6.115	1.46E-05
IFI27	6.333	4.280	4.00E-09	1.74E-05	5.884	1.74E-05
STAT1	5.454	7.882	4.90E-09	1.74E-05	5.851	1.74E-05
PSMB10	5.740	1.528	5.49E-09	1.74E-05	5.832	1.74E-05
GSTK1	1.552	5.890	5.77E-09	1.74E-05	5.823	1.74E-05
SP140L	6.125	0.465	8.51E-09	2.14E-05	5.758	2.14E-05
IRF1	7.278	4.265	1.65E-08	3.54E-05	5.646	3.54E-05
GBP1	12.308	2.693	2.08E-08	3.91E-05	5.606	3.91E-05
ISG15	5.142	4.931	2.92E-08	4.88E-05	5.546	4.88E-05
MT2A	3.091	4.452	3.97E-08	5.57E-05	5.492	5.57E-05
TNFRSF14	5.052	1.658	4.07E-08	5.57E-05	5.488	5.57E-05
IFI6	4.015	6.238	4.57E-08	5.73E-05	5.467	5.73E-05
ADAR	1.182	8.246	5.86E-08	6.02E-05	5.423	6.02E-05
SECTM1	7.449	0.609	6.01E-08	6.02E-05	5.419	6.02E-05
ERAP2	5.936	2.491	6.23E-08	6.02E-05	5.412	6.02E-05
ITK	8.431	-1.891	6.66E-08	6.02E-05	5.400	6.02E-05
MMP25-AS1	3.487	2.799	6.80E-08	6.02E-05	5.396	6.02E-05
XAF1	10.277	-1.583	8.11E-08	6.79E-05	5.365	6.79E-05
LAP3	4.017	6.512	9.33E-08	7.40E-05	5.339	7.40E-05

[1] False Discovery Rate
[2] Average expression of the gene in TMM-normalised $\log_2$ CPMs (counts-per-million).

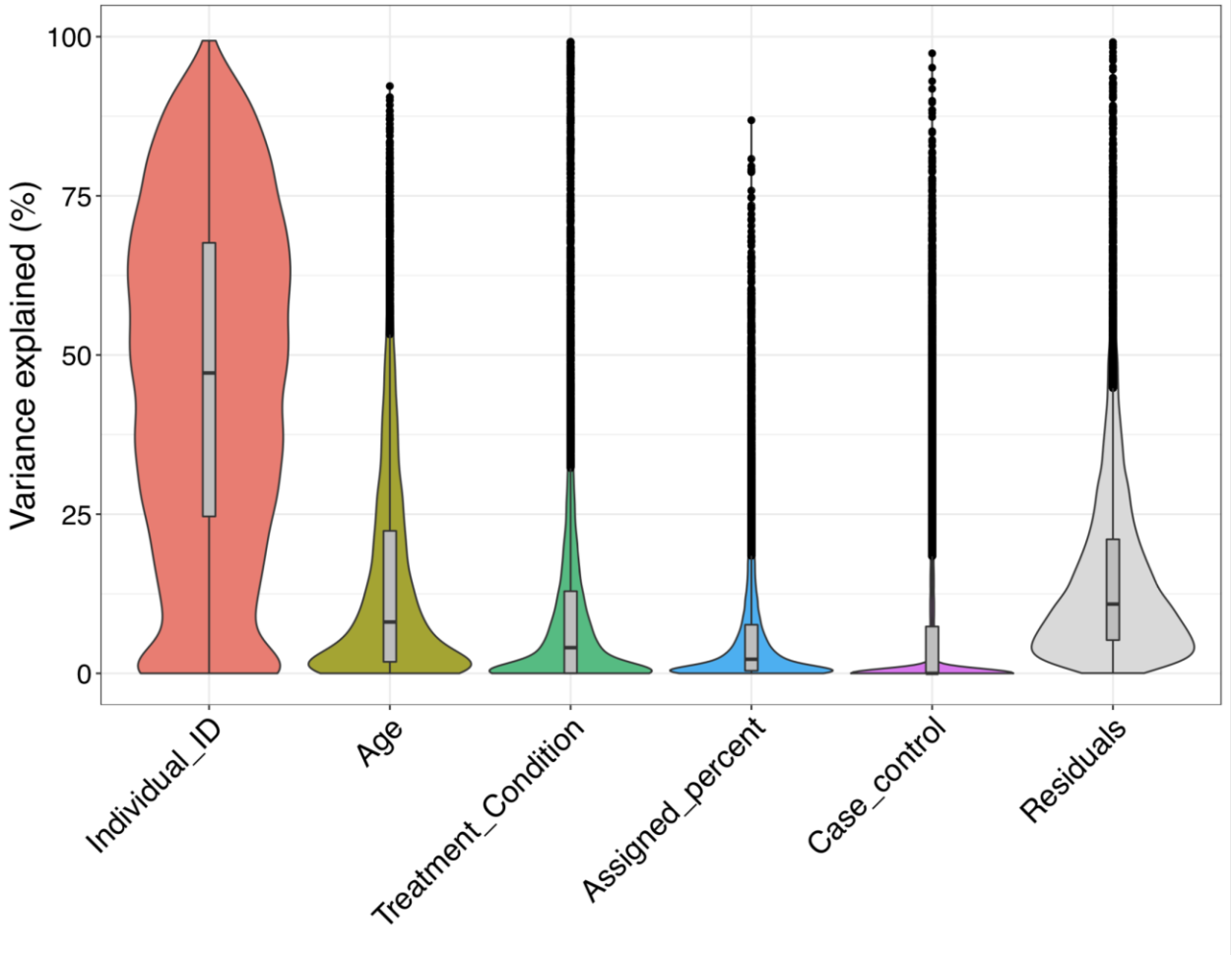
(Please see Supplementary Spreadsheets 3A-G for all genes included in the differential expression comparisons.



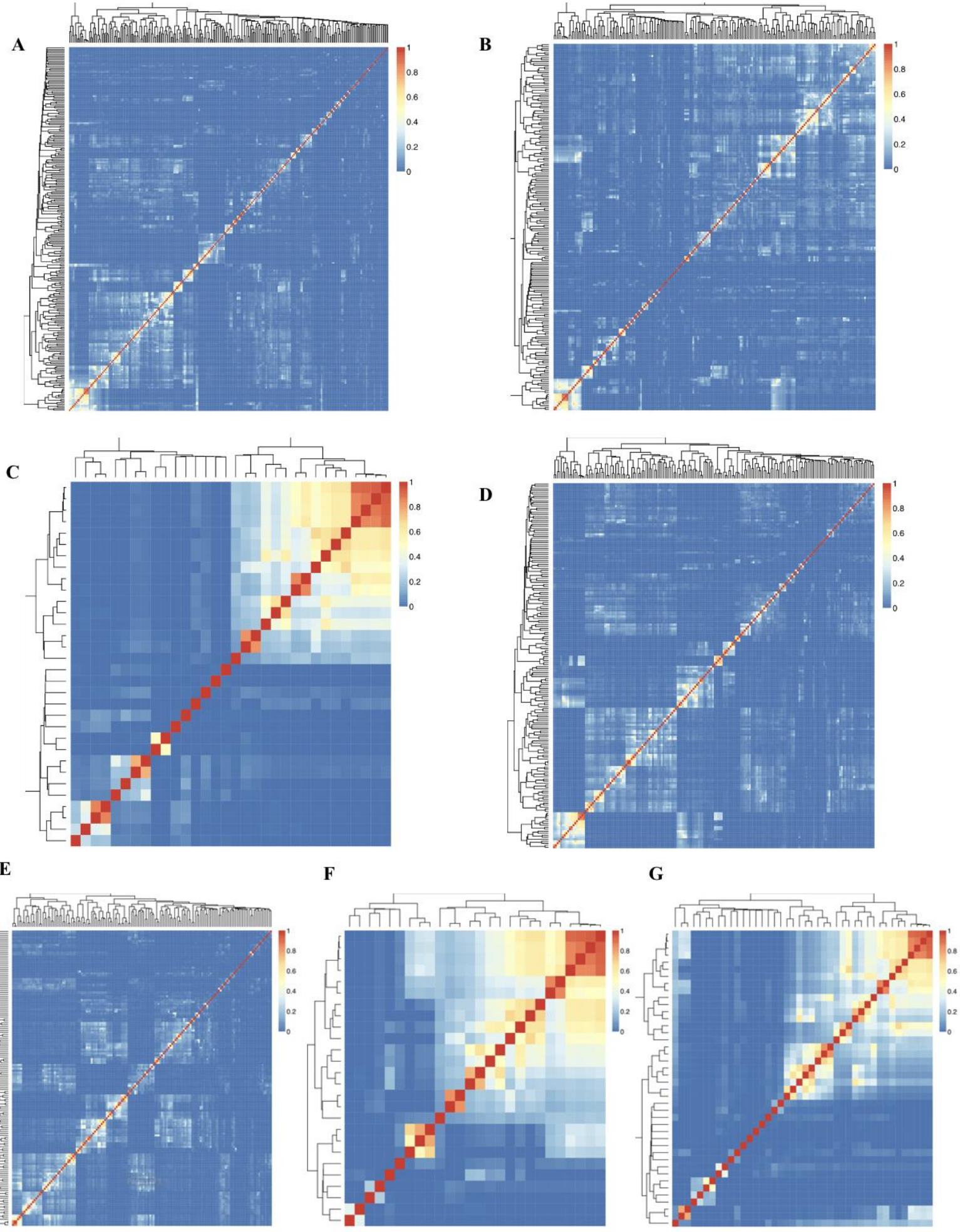
Supplementary Figure 1. *Validation of schizophrenia hiPSC lines.* **A.** Shows immunostaining of iPSCs for the pluripotency markers OCT4, SSEA4, NANOG and TRA-1-81. **B.** hiPSCs were further tested for their ability to generate cells from the 3 germ layers, as in Cocks et al (2014). All three of these hiPSC lines showed spontaneous generation of mesoderm, endoderm and (neuro-ectoderm cells. Validation of control lines used in this study has been shown in (Adhya et al., 2020; Shum et al., 2020).



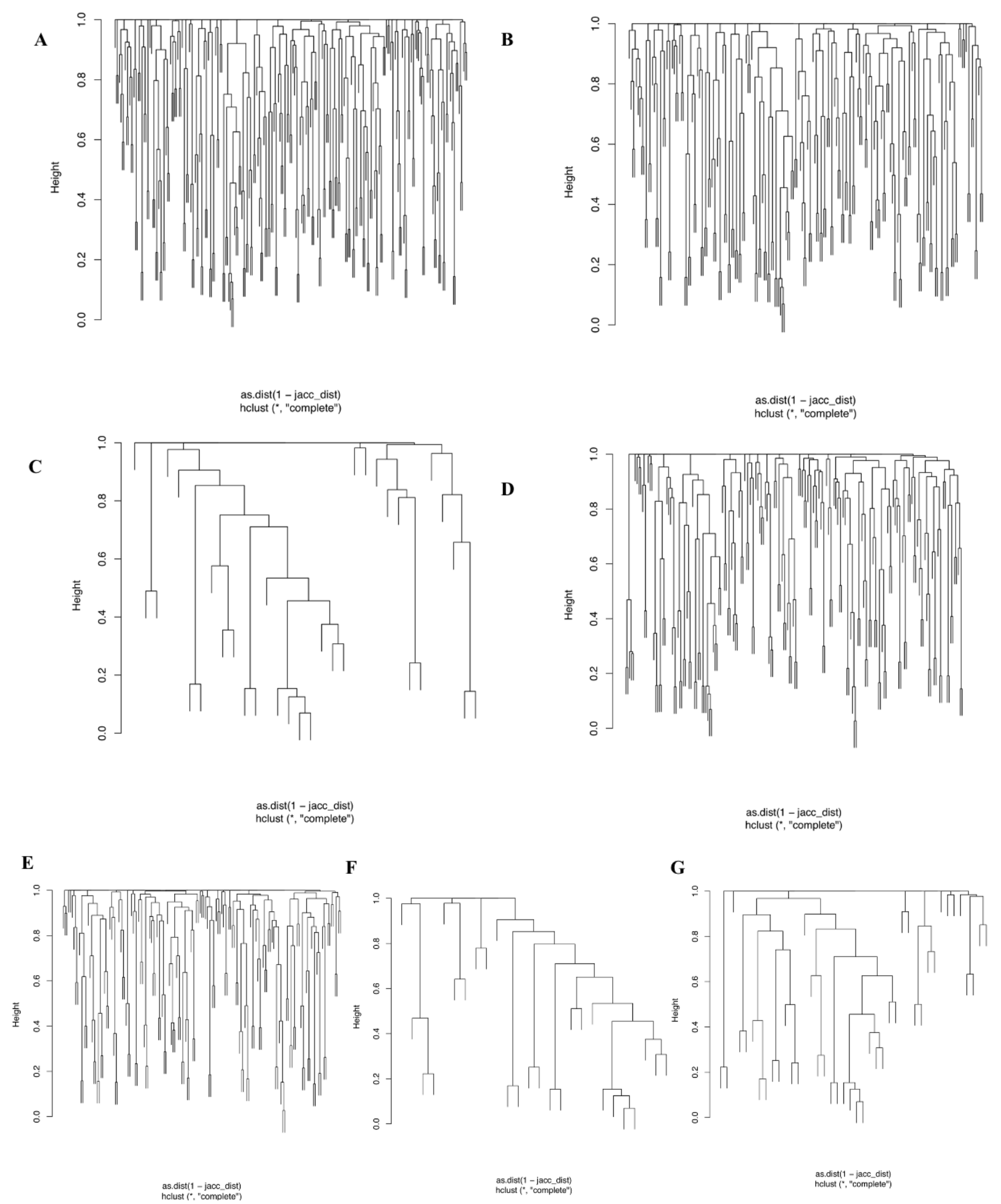
Supplementary Figure 2. *Principal component analysis (PCA).* The left panels show the relationship between PC1 and PC2; the right shows PC2 against PC3 (PC1 accounts for 86.55% of the variation in the data). **A.** By individual identifier. **B.** By treatment condition: IFNγ, IL-1β and vehicle (untreated). **C.** By diagnostic group (schizophrenia versus controls).



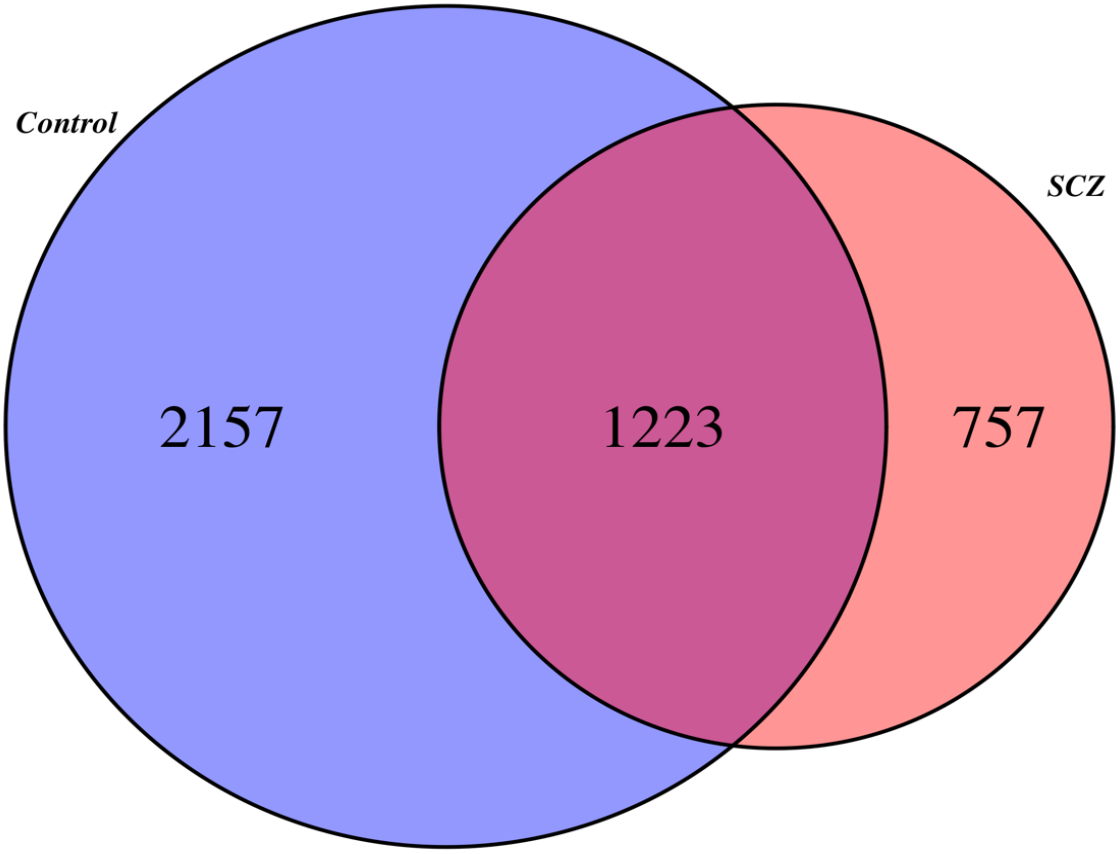
Supplementary Figure 3. *Variance partition analysis*. This shows the percentage of variance in the expression of each gene explained by each variable. Due to small sample size, this estimation may be very noisy. This figure mainly serves to illustrate that the primary source of variance in the data is the individual differences between each of the cell lines.



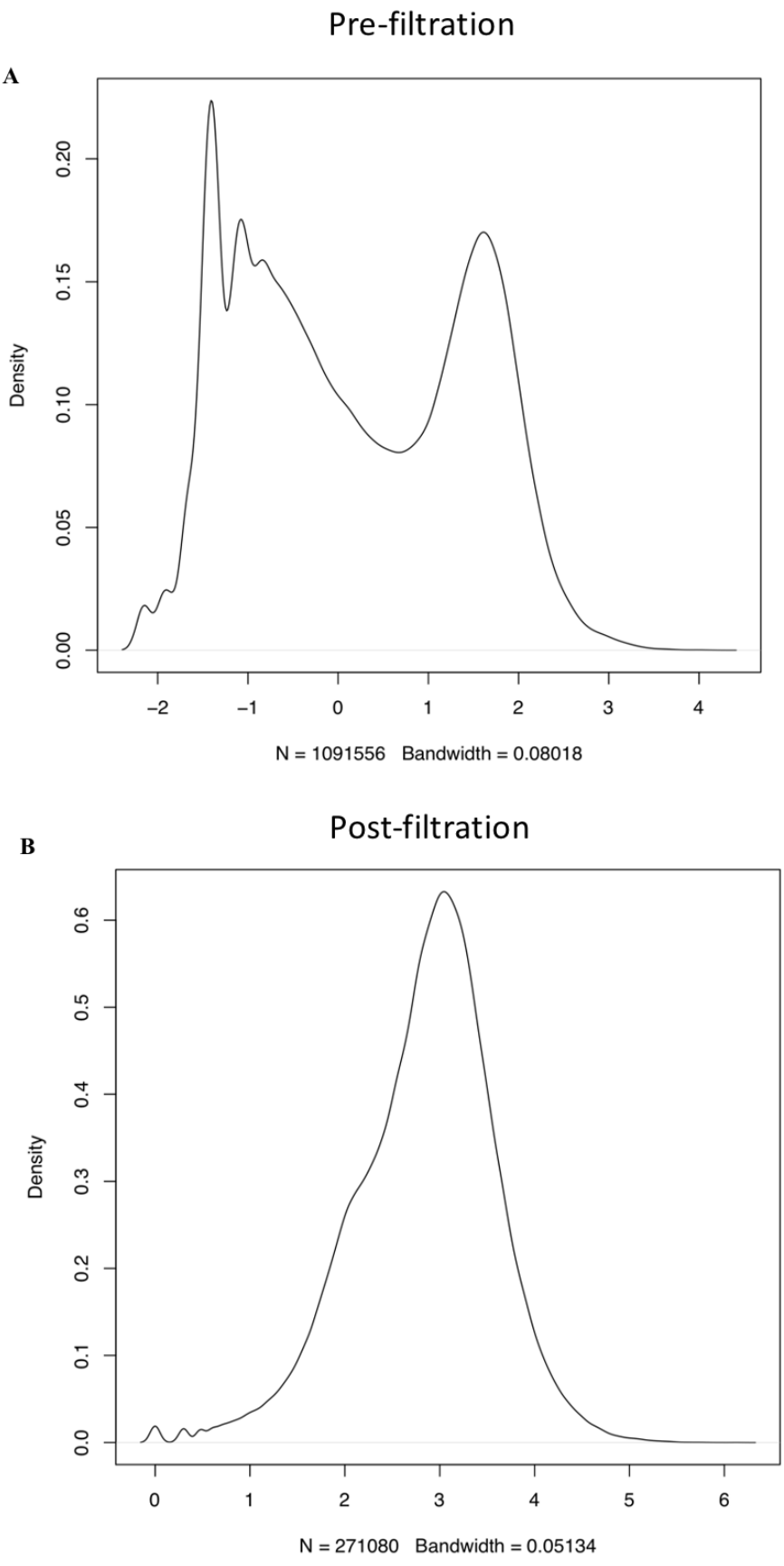
Supplementary Figure 4. *Jaccard similarity matrices* for signatures A-G, respectively.



Supplementary Figure 5. *Cluster dendrograms* for signatures A-G, respectively.



Supplementary Figure 6. *Venn diagram that shows the overlap between the genes that are differentially expressed in response to IFNγ in control cells and in schizophrenia cells.* Of the 4137 genes that respond to IFNγ in any of the two groups, only 1223 genes are in common, meaning that there are 2914 genes that appear differentially expressed in response to IFNγ in controls vs not in schizophrenia and vice versa.



Supplementary Figure 7. *Filtration to remove lowly expressed genes in order to minimise technical noise.* Plots **A** and **B** show the distribution of $\log_{10}$-transformed counts-per-million (CPMs) pre-filtration and post-filtration, respectively. Filtration threshold was set at $\log_{10}$CPM = 0.6 (CPM x $10^{0.6}$) by visual inspection, such that the filtered data showed an approximate Gaussian distribution.

Chapter 3

Why are psychiatric disorders and immune responses intertwined?

Abstract

There is a steadily growing literature on the role of the immune system in psychiatric disorders. So far, these advances have largely taken the form of correlations between specific aspects of inflammation (e.g., blood plasma levels of inflammatory markers, genetic mutations in immune pathways, viral or bacterial infection) with the development of neuropsychiatric conditions such as autism, bipolar disorder, schizophrenia and depression. A fundamental question remains open: *why* are psychiatric disorders and immune responses intertwined? To address this would require a step back from a historical mind-body dualism that has created such a dichotomy. I propose three contributions of active inference when addressing this question: *translation, unification,* and *simulation.* To illustrate these contributions, I consider the following questions. Is there an immunological analogue of sensory attenuation? Is there a common generative model that the brain and immune system jointly optimise? Can the immune response and psychiatric illness both be explained in terms of self-organising systems responding to threatening stimuli in their external environment, whether those stimuli happen to be pathogens, predators, or people? Does false inference at an immunological level alter the message passing at a psychological level (or vice versa) through a principled exchange between the two systems?

This chapter is adapted from Bhat, Parr, Ramstead & Friston, *Biology & Philosophy* (2021).

Introduction

In recent years, evidence for the interconnection between psychiatric disorders and immune responses has been accumulating rapidly (Nutma et al., 2019). So far, these advances have largely taken the form of correlations between specific aspects of 'peripheral' immunity (e.g., blood plasma levels of inflammatory markers) with the development of for neuropsychiatric conditions such as autism, bipolar disorder, schizophrenia and depression (Nudel et al., 2019). While these correlations speak to the interdependence of these two systems, there is less clarity in the literature as to why such a dependency should exist at all (Bennett & Molofsky, 2019). This relationship is further confounded by the fact that the brain, which is the primary physiological target of psychiatric research (David & Nicholson, 2015; Oertel & Kircher, 2010), has some specialised immune characteristics (such as microglia, a cell species responsible for mediating immunity in the brain), and is physically sequestered behind the blood-brain barrier – licensing the common belief that the brain is 'immune privileged' (Bennett & Molofsky, 2019). In essence, the question that remains unanswered is, *why* are psychiatric disorders and immune responses intertwined?

To address this would require a step back from a dualism (Descartes, 1641/1979), still subtly prevalent in modern medicine and contemporary philosophy (Gendle, 2016; Glannon, 2020; Mehta, 2011; Morris, 2010; Putnam, 1960, 1967) between the mind (and often, in concordance, the brain) and the body. The complexity of the human brain, and its intimate relation to our conscious experience, makes it easy to forget that it is, nevertheless, an organ in service of maintaining the integrity of the body it inhabits. To reject this dualism is to view the mind as embodied, and the brain as a part of the living body (Varela et al., 1991).

The ripples of effect that pass between the brain and the immune system (Blalock, 1984) are less surprising, however, under the hermeneutic perspective (Friston & Frith, 2015; Gadamer, 1976) supplied by the free energy principle (FEP) (Friston, 2005, 2009), in which autopoiesis – or self-evidencing (Clark,

2013; Hohwy, 2013) – is a constant process at every organismal level (cells, tissues, organs, organisms, societies), as well as a fundamental motivational drive. In this light, the brain and the immune system share a common imperative: to distinguish consistently and accurately between 'self' and 'non-self' or 'threatening' and 'non-threatening' to the individual as a whole. The multiscale perspective afforded by the free energy principle means this disambiguation between self and other is constrained by the hierarchical level (i.e., spatiotemporal scale) above (Hesp et al., 2019; Kirchhoff, 2018; Kirchhoff et al., 2018; Palacios et al., 2020; Ramstead et al., 2018; Ramstead et al., 2019) – a necessary facet of 'belonging to something greater'. On a general note, this thesis rejects dualism in the same spirit of recent proposals – from molecular biology (Kuchling et al., 2019; Manicka & Levin, 2019) to evolution (Ao, 2005; Campbell, 2016; Frank, 2012; Ramirez & Marshall, 2017) – that put inference, beliefs[12] and purpose into biological processes.

In this chapter, I propose that an appeal to the FEP, and its corollary, active inference, is useful for explaining the relationship between the immune system and the brain in three important ways: *translation*, *unification*, and *simulation*. I will unpack this in five parts. In the first two sections, I briefly overview active inference and the human immune response. In the third, I explore insights that may be gained by translating the immune response into the language of active inference. In the fourth, I explain how understanding the brain and immune system as components of a larger Markov blanket explains their relationship in terms of a shared imperative and propose a 'diaschisis of threat' model that may elucidate the overlap between autoimmune and psychiatric disorders. In the fifth, I demonstrate the benefits of formulating these ideas in the form of generative models.

[12] In this chapter, 'beliefs' should be read as Bayesian beliefs – in the sense of Bayesian belief updating and belief propagation. In other words, beliefs are simply posterior or conditional probability distributions, usually encoded by the physical state of a person or particle. They are not propositional beliefs of a pre-theoretical sort. See below for more detail on Bayesian beliefs.

Active inference and the Free Energy Principle

The Free Energy Principle (FEP) is a formalisation and extension of Schrödinger's (1956) seminal observation that living organisms are defined by the avoidance of entropy – in other words, they 'self-organise', or maintain homeostasis. Supplied by the mathematics of nonequilibria, it emerges that all self-organising (and therefore biological) systems are fundamentally driven to minimise a quantity called 'free energy' – which can be heuristically understood as a measure of unlikeliness[13].

Active inference is an application of the FEP to sentient behaviour. It specifies that self-organising systems, in addition to adapting to their environment, can also *act* upon it so that it conforms to their internal generative model of the world (Friston et al., 2010; Parr & Friston, 2018a, 2019). An internal model is a probabilistic account of how sensory data are generated – normally comprising a prior (how probable is a hypothesis before making any observations) and a likelihood (how likely are observed data under that hypothesis). For more sophisticated systems, this model may represent sequences through time, making it possible to select 'policies' (*sequences* of actions) that minimise '*expected* free energy' – which (heuristically) is the free energy expected on pursuing a policy. Some of these terms may seem somewhat anthropomorphic. This is because the origins of active inference were in application to the human brain, building upon Helmholtz's (1866/1962) ideas about 'unconscious inference' and 'predictive coding' (Knill & Pouget, 2004; Rao & Ballard, 1999), which equates free energy minimisation with 'prediction error minimisation', or 'belief updating'[14].

These frameworks rest upon a characterisation of the brain as 'Bayesian', in reference to Bayes' Theorem. Reverend Thomas Bayes' equation (Equation 1), first published in 1763, is a simple but

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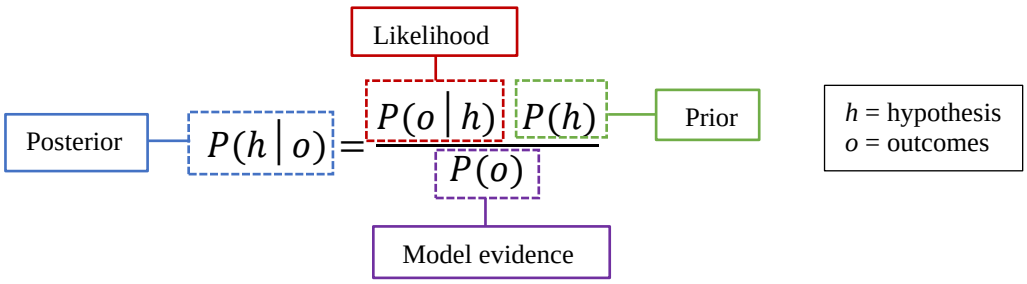
[13] Strictly speaking, variational free energy is more generally an upper bound on surprisal, a.k.a. self-information; namely, the log probability that any given person or particle will be found in a particular state. In Bayesian statistics, negative self-information is also known as log evidence. Therefore, minimising free energy maximises evidence; hence, self-evidencing.

[14] The updating of the generative model depends on a weighing up of the relative 'precision' of prior beliefs and sensory evidence, similarly to how a scientist would weigh up new evidence against a body of literature. Here, 'precision' is a measure of certainty, thought to be synonymous with gain (excitability) of post-synaptic pyramidal neurons reporting prediction errors ((Parr & Friston, 2019))

profound formula for determining conditional probabilities (Bayes, 1991). In essence, Bayes' Theorem considers the probability of an outcome (or 'posterior belief') to be dependent not just on cross-sectional evidence but also prior knowledge ('prior beliefs'). For example, if I lose my sense of smell ('anosmia') and want to know whether this is caused by a SARS-CoV-2 infection ('Covid19') (the hypothesis, *h*) as opposed to a vitamin B12 deficiency (the alternative hypothesis), I could use Bayes' Theorem. This would give me a 'posterior belief', $P(h|o)$, which here is the probability of having Covid19 given the loss of smell. There are three components that I would have to combine to arrive at my posterior belief:

1. My **prior beliefs** about the probability of having Covid19, $P(h)$.
2. The **likelihood** of observing the symptom given the infection, $P(o|h)$.
3. The **model evidence**: all the possible reasons for having lost my sense of smell, $P(o)$.



Equation 1a. Bayes theorem. In this formula, each term in the equation has a specific name as labelled above. *Prior beliefs* are beliefs about the hypothesis (about the cause of the observation) – e.g., how probable is it for a person to have Covid19? If 20% of the population are estimated to be infected, we could say $P(h)$ here is 0.2. The *likelihood* represents how likely I am to observe this in the context of my hypothesis. E.g., How likely is it for a person to lose their sense of smell if they have Covid19? If 86% of people with Covid19 experience a loss of smell, we could say $P(o|h)$ here is 0.86. The model evidence is 0.175 as explained under Equation 1b, so this gives a posterior belief of (0.86 x 0.2)/0.175 = 0.98 (i.e., based on these population estimates, my anosmia is much more likely due to Covid19 than a B12 deficiency!)

So, at a given time point (*t*), prior beliefs are combined with observed outcomes to become posterior beliefs. This process is known as 'belief updating'. For the sort of recurrent belief updating that underlies self-organisation, the posterior beliefs of one moment (*t*) become the prior beliefs of the next (*t*+1). The internal/generative model that underlies this sort of recurrent belief updating over a series of discrete time-points (*t*, *t*+1, *t*+2...*t*+*n*) is often represented as a Markov Decision Process model (e.g.,

Figure 4) (Mirza et al., 2018; Mirza et al., 2016). Internal/generative models that update beliefs in a continuous fashion are often presented as predictive coding-style models (e.g., Figures 2 and 3) (Kanai et al., 2015; Parr & Friston, 2018b). The former is applicable, for example, to decision-making, wherein the individual must decide between several discrete courses of action; the latter is applicable, for example, to movement wherein the individual must extend or flex muscles (Parr & Friston, 2018b). In both cases, belief updating can be described using Bayes' simple theorem.

In other words, the brain is seen here as an inference machine that makes sense of the world – and adapts to a constantly changing environment – by drawing associations between observations. This generally involves determining the probability of an uncertain cause given some observed evidence. These observations come in the form of sensory 'data' received by our sensory receptors (e.g., pressure sensed by Pacinian corpuscles or vibration of the eardrum on interaction with sound waves). For example, if we hear the sound of an instrument from another room, the pitch, timbre and tone of the sound (the sensory data) allow us to infer what sort of instrument it is (the uncertain cause) (Figure 1). Much of this inference occurs subconsciously – hence Helmholtz's term 'unconscious inference' (Helmholtz, 1866/1962) – and involves an implicit Bayesian hypothesis test. Bayesian hypothesis testing differs from classical/frequentist hypothesis testing in that Bayesian methods do not necessitate a universal 'cut-off' point such as $p = 0.05$, below which the null hypothesis is rejected. Instead, the Bayesian method of hypothesis testing is Bayesian model comparison, which involves defining several models that may explain the observed [sensory] data and comparing them – the 'winning' model being the one that best predicts observations.

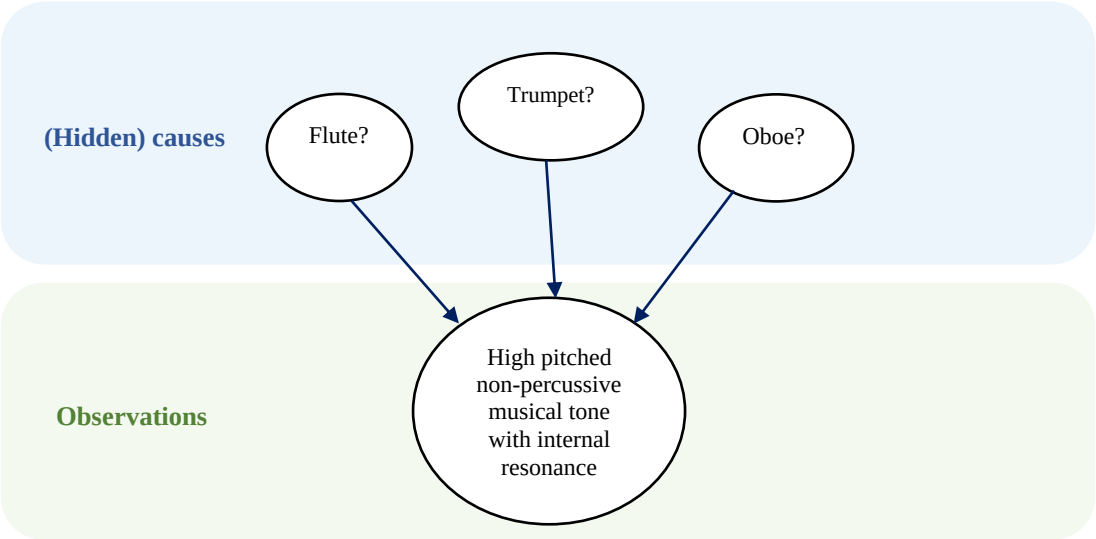


Figure 1. Three potential (independent) hidden causes of sensory observations. The arrows (or 'edges') here represent a conditional dependence between the observed sensory data and the potential hidden cause. The causes are 'hidden' because we do not have direct access to the world, but rather interpret it through our senses. Therefore, each of these hidden causes correspond to alternative 'hypotheses' about the causes of the sensations. The conditional dependences in turn correspond to the 'likelihood' (from Bayes Theorem as shown in Equation 1a).

Model evidence is key to hypothesis testing under Bayes' Theorem. It refers to the likelihood of the outcome given *all* possible hypotheses – i.e., the hypothesis space. Mathematically, model evidence is the sum (or integral, in the case of continuous outcomes) of the likelihood times the prior, over all possible hypotheses (Equation 1b). In other words, this is the term which accounts for alternative hypotheses.

$$P(o) = \sum_{h \in H} P(o|h)P(h)$$

h = hypothesis
H = the set of all hypotheses
o = outcomes

Equation 1b. Model evidence. The evidence term in the denominator of Equation 1a. equates to the numerator (likelihood x prior) summed over **all** hypotheses. In this case, there are two possible hypotheses about the causes of the loss of smell: Covid19 or vitamin deficiency. If 5% of people with B12 deficiency tend to exhibit anosmia, and 6% of the population have B12 deficiency, the model evidence would be: $P(\text{anosmia}|\text{Covid19})\ P(\text{Covid19}) + P(\text{anosmia}|\text{B12 deficiency})\ P(\text{B12 deficiency}) = 0.86 \times 0.06 + 0.05 \times 0.06 = 0.175$

Note that the model evidence is very difficult to compute when the hypothesis space is large (as it would be if we were to consider *all* the possible reasons for having anosmia), or if the hypotheses were overlapping (i.e., a person loses their sense of smell because they have *both* Covid19 and a B12 deficiency). This is usually the case with sensory information processed by the brain, so model evidence in this context is generally considered an approximation (Fourment et al., 2020). Indeed, *maximising* model evidence is synonymous with minimising free energy (Demekas et al., 2020; Friston, 2009).

Under active inference, the internal dynamics of a biological system can therefore be understood as solving an inference problem using sensory data. Combing prior beliefs with the likelihood associated with sensory data, gives a posterior belief; namely, the probability of some explanation of observed sensory data. Behaviour is guided by these inferences (Rick A. Adams et al., 2013; K. Friston & C. Frith, 2015; Friston et al., 2010). Identifying the inference problem that the system is solving supplies an explanation, in the form of a generative model, that underwrites optimal behaviour. In a sense, this approach represents a formal rejection of Cartesian dualism in favour of a Markovian Monism (Friston et al., 2020). The first step in trying to understand the inference problem a system is implicitly solving is to define what is meant by 'a system'. The statistical construct of a 'Markov blanket' (Pearl, 1988) is typically applied to delimit a self-organising system, by rendering the internal components of the system conditionally independent from its environment, while accommodating a vicarious communication between the inside and the outside[15]. This bidirectional communication is wrought by dividing the blanket into unidirectional influences that are either sensory (e.g., from pathogen to immune system) or active (e.g., from immune system to pathogen).

Further, under the Complete Class theorem (Daunizeau et al., 2010; Wald, 1947), any behaviour can be rendered Bayes optimal given the appropriate prior beliefs. This means that defining the 'inference

[15] Technically, the reciprocal exchange between the inside (internal) and outside (external) across the Markov blanket means that the system is 'open', which calls on a very general formulation from physics in terms of nonequilibrium steady states (Friston, 2019).

problem' can also help to explain (by lesioning the optimal generative model) maladaptive behaviours, such as might be seen in autoimmune or psychiatric disorders. This approach has been applied fruitfully to explain – for example – visual neglect (Parr & Friston, 2018a), hallucinations (R. A. Adams et al., 2013; Benrimoh et al., 2019) and failures of interpersonal communication (Moutoussis et al., 2014).

The implication for philosophy here is support from the physics of biology for a hermeneutic perspective (Friston & Frith, 2015; Gadamer, 1976) of constant (and imperfect) energetic dialogue between an organism and its environment; and a relativism wherein normality is context dependent, perception is deeply subjective and absolute objective reality is unattainable.

A primer on immunology

The human immune system is a sophisticated, multi-organ system that fights infection, prevents cancer, eliminates harmful substances, regulates inflammation and supports wound healing (Marshall et al., 2018; Murphy et al., 2012; Portou et al., 2015). It performs these functions by recognising tissue damage, differentiating 'self' from 'nonself', and destroying any foreign or toxic material. At the centre of this system are white blood cells, that move around the body through a network of delicate tubes and nodes, together called the lymphatic system (Murphy et al., 2012). On encountering disease-causing organisms, or pathogens – such as viruses, bacteria and parasites (Chaplin, 2010; Murphy et al., 2012) – they enact an immune response. Two key types of white blood cells are macrophages (that engulf and dissolve pathogens and infected cells – a process known as phagocytosis); and lymphocytes, which further subdivide into B-cells and T-cells. T-helper cells (which are positive [+] for the cell surface glycoprotein 'cluster of differentiation' 4, or CD4), release cytokines (molecular 'alarm' bells that can initiate or attenuate an immune response); cytotoxic T-cells (with the surface marker CD8) can directly neutralise pathogens (Murphy et al., 2012). In health, these exist in a ratio of CD4+ to CD8+ T-cells of approximately 2:1 (McBride & Striker, 2017). B-cells subdivide into plasma cells, which produce

antibodies, and memory cells, which remember previously encountered antigens in case of future infections (Chaplin, 2010; Marshall et al., 2018; Murphy et al., 2012).

Innate immunity

The innate component of the immune system mounts a relatively non-specific inflammatory response, which is tuned by the adaptive system. It comprises immune molecules and cells that detect, attack, and engulf pathogens. A useful starting point in understanding this system is the complement pathway: a series of 'molecular dominoes' that trigger a cascade of events designed to neutralise any pathogens. The molecules that comprise complement system are plasma proteins known as *complement components*, denoted as 'C1, 'C2', 'C3', and so on (Murphy et al., 2012). Each of these has a unique role, as outlined below.

There are three ways in which this cascade may be triggered (Chaplin, 2010). The first is known as the *classical* pathway, and rests upon binding of complement component C1q to IgG or IgM antibodies[16]. The implication here is that, in the presence of a pathogen identified by the adaptive arm of the immune system, there will be a high density of antibodies to which C1q may bind[17]. This leads to a localised increase in activity of the classical pathway. The second complement pathway is the *alternative* pathway, which is tonically active – possibly embodying a belief about the prior probability of infection. The third is the *lecithin* pathway. Like the classical pathway, the lecithin pathway is triggered by the binding of endogenous molecules (mannose binding lecithin) to antigens (mannose) on the surface of pathogens. Crucially, this does not require the production of antibodies by the adaptive immune system. One interpretation of this pathway is in signalling the likelihood of infection. The presence of mannose indicates a high likelihood, while its absence indicates a low likelihood.

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[16] Antibodies are divided into several classes depending upon their structure. These are (in order of prevalence) IgG, IgA, IgM, IgD, and IgE (where Ig means 'immunoglobulin'). An individual antibody is made up of two structural components referred to as Fab (fragment antibody binding) and Fc (fragment crystallisable) regions.

[17] C1q is broken down by C1-inhibitor. Absence of the latter underwrites the excessive activation of the complement pathway that characterises hereditary angioedema (Busse & Christiansen, 2020)

These three pathways converge upon the C3 convertase enzyme, which breaks C3 down into C3a and C3b. C3a sets in motion events that facilitate immune cells entering the tissues from the blood. It does so through triggering degranulation of mast cells in the tissues[18]. These release histamine that acts to increase vascular permeability (Ashina et al., 2015). C3b inhibits further action of C3 convertase, while additionally triggering the breakdown of C5 into C5a and C5b. C5a acts as a chemoattractant for circulating neutrophils, which pass through the permeable vasculature into the tissues. C5b joins forces with C6, C7, C8, and C9 to form the membrane attack complex, which is used to punch holes in the surface of the pathogen. The neutrophils (and tissue macrophages) engulf the pathogen through a process known as phagocytosis and produce reactive oxygen species to kill these pathogens[19]. Tissue macrophages may respond to pathogens independently of the complement pathway as they (like C1q) can sense the presence of Fc regions on IgG and IgM antibodies (Chaplin, 2010; Murphy et al., 2012). Foreshadowing some of Section 3, this could be interpreted as an example of an action-perception cycle, where increased C3 convertase activity corresponds to a primitive kind of percept, whose (active) consequences are the neutralisation of pathogen.

Adaptive immunity

There are several points at which the adaptive arm of the immune system tunes this response. It does so by producing antibodies (also known as 'immunoglobulins'), which are Y-shaped proteins produced by plasma cells. Each tip of the 'Y' has a binding site with a unique structure, allowing each antibody to bind with high specificity to 'antigens', which are unique molecules on the surface of (or released by) cells and microorganisms. The specificity of this binding acts as a 'lock-and-key' mechanism that can

[18] Mast cells may also be triggered directly by the presence of a pathogen, via the IgE antibodies on their surfaces.
[19] The killing of pathogens inside neutrophils (and macrophages) depends upon the NADPH oxidase enzyme. Congenital absence of this leads to an immunodeficiency called Chronic Granulomatous Disease ((Arnold & Heimall, 2017) Granulomas are groups of phagocytic cells, normally macrophages, that have engulfed a pathogen but are unable to kill it. These also occur in conditions like tuberculosis (where the mycobacterium is resistant to oxidative killing) or sarcoidosis.

identify antigens, and mark known pathogenic or unknown antigens for destruction by macrophages. Once pathogens are coated with antibody, all the events outlined in the previous subsection are initiated. The presence of specific antibodies favour increased classical complement pathway activation (perhaps acting as an 'empirical' prior for this system[20]), increased degranulation of mast cells, and increased phagocytosis by tissue macrophages in response to specific antigens (Murphy et al., 2012).

A good place to start in reviewing this system is the Major Histocompatibility Complex (MHC), also known in humans as the Human Leukocyte Antigen (HLA)[21]. MHC mostly comes in two flavours (I and II). MHC-I is found on the surface of almost all somatic cells (Murphy et al., 2012). Once a cell has become infected by an intracellular pathogen, it uses the MHC-I to display antigens from that pathogen on its surface. MHC-II is used similarly but is only present on the surface of specialised immune cells that engulf and phagocytose pathogens (Chaplin, 2010). These include macrophages, B-cells, and dendritic cells – collectively known as antigen presenting cells (APCs).

The MHC-I pathway allows an arm of the adaptive immune system to interact directly with pathogens, without needing to go through the innate immune system. These mechanisms occur in peripheral tissues and circulation. T-cells with surface CD8 receptors bind to the MHC-I and, if the antigen presented by this molecule matches the specificity of that cell's T-cell receptor (TCR), the CD8+ T-cell releases perforin, granulysin and granzyme, which trigger the death of the infected cell. The MHC-II system sits a level above the innate and MHC-I systems (Zhang et al., 2014). Once the innate immune system has enabled various APCs to engulf pathogens and display their antigens via MHC-II, these cells travel to lymph nodes where they are met by CD4+ T-cells. Like CD8+ cells, these have antigen-specific

[20] Empirical priors are Bayesian beliefs derived from higher levels of a hierarchical model. For example, a group mean may provide an empirical prior over an individual's response to some treatment in classical (mixed effects) analyses of experimental data.

[21] Given their central role in functioning of the adaptive immune system, it is unsurprising that certain HLA subtypes are associated with clusters of diseases with autoimmune features. Perhaps the most famous association is that of HLA-B27 with a group of disorders that includes psoriasis, ankylosing spondylitis, inflammatory bowel diseases, and reactive arthritis (Bowness, 2015).

TCRs that bind to MHC-antigen complexes but are selective for MHC-II. On binding, CD4+ T-cells differentiate into Th1 or Th2 cells, depending upon whether they are dealing with an intracellular or extracellular pathogen, respectively.

Th1 cells release interferon-γ (IFNγ) that triggers macrophages to destroy any pathogens they have engulfed. In addition, they induce antibody production by B-cells. Th2-cells recruit Eosinophils[22] through interleukin (IL) 5 secretion, and promote isotope switching in B-cells through IL-4 signalling. Heuristically, the Th1 effect over B-cells is to increase specific antibody production. The Th2 effect is to broaden the distribution of antibody specificities (Murphy et al., 2012).

The process of B-cell activation by a Th1-cell occurs in lymphoid tissue. B-cells in the periphery bind to a pathogen via their B-cell receptor (a membrane bound antibody) and endocytose it. As outlined above, they present antigens to Th1-cells via MHC-II. On binding of the TCR to MHC-II, the T-cell presents a CD40L molecule that binds to the B-cell CD40 surface molecule (Elgueta et al., 2009). This stimulates the B-cell to differentiate into either a plasma cell (secreting antibodies) or a memory cell (a simple form of immunological plasticity). Although T-cell independent B-cell activation is a well-recognised phenomenon, this is outside the scope of this chapter. The presence of antibodies towards a specific antigen effectively orients the complement system (via the classical pathway) to respond with greater amplitude to that antigen (Chaplin, 2010). An analogy in cognitive sciences might be attentional orientation towards a visual stimulus, directed by descending messages from higher to lower cortical regions (Büchel et al., 1998; Buschman & Miller, 2007). For more detailed overviews of the immune response, please see Marshall et al. (2018) and Murphy et al. (2012)

[22] Immune cells specialising in defence against multicellular parasites and implicated in various hypersensitivities

Translation

Although the primary focus of the active inference literature so far has been the human nervous system, the immune system is a similarly complex dynamic system that may be explained using the same mechanics (Parr et al., 2020). In this section, I first present an example of translation of the immune response, as described above, into the language of active inference. I then present an example of what this may lend to the study of immunology.

The Markov Blanket

As mentioned above, the first step in identifying the inference problem a system is solving is defining the limits of the system (i.e., the Markov blanket) and its active and sensory components. In the (simplified) immune response described here, the innate immune system 'senses' extracellular pathogens through Fc-regions of antibody (IgG or IgM) bound to specific antigens, binding of IgE antibodies on the surface of mast cells to pathogenic antigens, or through detection of cell-surface molecules such as mannose by mannose-Binding lecithin. Intracellular pathogens are sensed via binding of T-cell receptors to cell surface Major Histocompatibility Complex (MHC). For most cells, this is MHC I. For antigen presenting cells (including macrophages, dendritic cells, and B-cells), MHC II may also be used. This suggests at least three sorts of sensory influences:

1. mannose-binding lecithin
2. Specific antigens
3. MHC-I

These sensory data are generated by external states comprising the specific pathogen, the presence of mannose on the surface of the pathogen, and whether a pathogen is intracellular or extracellular. There are many other molecules and sensors that play a role in detection of pathogens, but I focus upon the above three.

Active influences on these external states include release of molecules by CD8+ T-cells that lead to death of cells with intracellular pathogens. This leads to a decrease in antigen-presenting MHC-I sensory influences. In addition, the membrane attack complex from the complement pathway acts to kill pathogens in a relatively non-specific way, depleting both specific antigens and local concentrations of mannose-binding lecithin. Finally, extracellular pathogens are depleted by the action of macrophages and neutrophils that engulf these cells.

The three active influences I will focus upon are:

1. CD8+ T-cell molecules (perforin, etc.)
2. Membrane attack complex
3. Macrophages and neutrophils (phagocytosis)

The interactions between the three sensory and active influences I have identified may be thought of as analogous to spinal and brainstem reflexes of the sort found in the proprioceptive branches of the nervous system. Changes in the sensory aspect induce changes in the active part that restores sensations to some set-point. In the nervous system, the set-point depends upon descending signals from the brain that may be thought of as predictions (Rick A. Adams et al., 2013) of the proprioceptive consequences of the desired (i.e., anticipated) movement. In the field of motor control, this is known as the equilibrium point hypothesis (Feldman & Levin, 2009).

The generative model

Once the active and sensory states of the system have been defined, the challenge is to find the generative model that accounts for the dynamics of internal and active states[23]. The model should specify which

[23] Technically, the internal and active states constitute *autonomous* states, in the sense that they do not depend upon external states. Crucially, one can always express their dynamics as a gradient flow on variational free energy. Heuristically, these gradients often have the form of prediction errors; namely, the difference between a sensory state and the prediction of that sensory state based upon the internal states. In other words, both internal and active states trying to minimise prediction errors;

explanatory variables (external states) conspire to generate the sensory states. As shown in Figure 2, the entirety of the second section of this manuscript can effectively be condensed into a single model and its inversion. Note that Markov blanket is an informational separation from the environment – it does not necessarily correspond to physically materialised boundaries (Kirchhoff et al., 2018; Palacios et al., 2020). The Markov blanket shown below is not comprised of a cell or tissue membrane but elements of the immune system (e.g., perforin molecules, macrophagic cells) that mediate the interactions with the pathogen. From this perspective, everything shown above the Markov blanket in Figure 2 is the set of external states that generate the sensory states shown within the blanket. The dynamics of internal states (depicted below the blanket) can then be interpreted as drawing inferences about the external states, which then influence the active states in the Markov blanket.

either by changing the internal milieu to adapt to sensory fluctuations or by acting upon the external milieu to realise predicted sensory states.

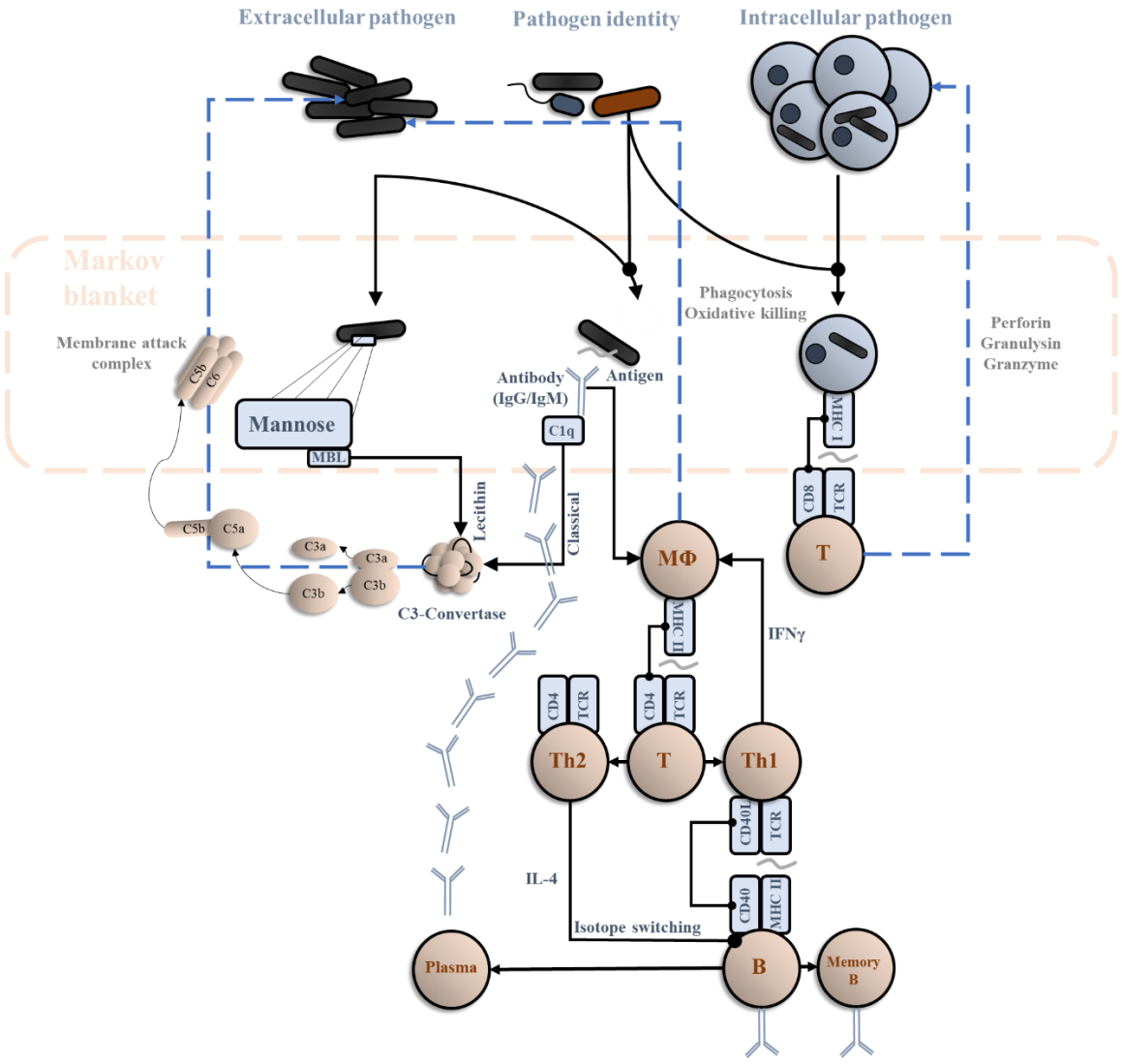

Figure 2. Immunoceptive inference. This schematic shows a simplified account of an immune response to foreign pathogens. It is arranged in the style of graphics used in computational neuroscience – and machine learning – to show a data-generating process comprising external states (here, the identity of the pathogen, and the intracellular and extracellular pathogen concentrations), the sensory data they generate (mannose, specific antigens, and MHC-I antigen presentation), and the message passing in the internal system – whose role is to draw inferences about external states and select actions that correct deviations from a desired state. The dashed blue lines emphasise the influence the internal states exert on external states (via active states). Note the resemblance between these and the simple reflex loops associated with movement generation in the spinal cord. The implication of this graphic is that one think of the internal states that influence these responses as like the neurons of the central nervous system, forming inferences about the outside world through message passing among different populations. One perspective on this is that the concentration of CD8+ T-cells represents an implicit belief about the number of infected cells, the concentration of macrophages (and activated C3-convertase) a belief about the number of extracellular pathogens, and the CD4+ T-cell to B-cell to plasma cell loop an example of message passing to identify the pathogen identity to direct ‘attention’ towards the appropriate antigens.

Sensory attenuation in the immune system

If indeed active inference is a universal framework across self-organising systems, it stands to reason that key aspects of brain-based sentience explained by active inference may possess analogues in the immune system. This was hinted at in Section 2 but unpack this in greater depth here. For example, the phenomenon of sensory attenuation (Brown et al., 2013) has drawn upon the notion, under active inference, that a system cannot act without temporarily attenuating the precision (gain) of the consequences of its own actions. This is because attenuating sensory precision effectively allows the system to 'ignore' the prevalent sensory evidence that "I am not acting", thereby permitting a posterior commitment to the prior prediction, "I am acting". These predictions are fulfilled by motor, autonomic or possibly immunological reflexes to realise the predicted sensory state of affairs. It is therefore action that, ultimately, updates the internal model, through an exchange with the external world (K. Friston & C. Frith, 2015).

If sensory attenuation possesses an immunological analogue, there may be a great deal to be learned by translating what has already been well-studied in the domain of neuroscience to the domain of immunology. If this is not the case, there is another, equally interesting avenue to be explored, in the form of the question, "What is different about the nervous system that makes its actions dependent upon sensory attenuation, when the actions of other physiological systems are not?" In addition, this kind of translation may serve as a sanity check of sorts for claims made under the active inference framework.

To exemplify this, let me propose a plausible immune analogue. There will generally be an immune response triggered by the proliferation of allogenic cells and tissue damage in the body. However, there are some notable instances, such as pregnancy, when the body must tolerate the proliferation of allogenic cells and some degree of tissue damage, up to a certain threshold – at which labour is initiated. In order to allow a foetus to grow, it could be said that there must be an attenuation of the 'sensory' consequences (e.g., MHC-I presentation, which initiates an immune response) of self-

generated proliferation. Indeed, foetal tissue is one of the few somatic tissues whose cells exhibit significantly reduced MHC-I presentation (Gaunt & Ramin, 2001). Given the model above, it would be possible to start to explore this possibility by, for example, reducing MHC-I presentation as a sensory state. I intend to expand on this angle in future work.

The usefulness of drawing such an analogy is in effectively 'stealing' dynamic characteristics of Markovian systems from previous work. We are still in very early stages of understanding the profound immunological consequences of pregnancy. Sensory attenuation has been relatively well studied in the nervous system, and there may be significant insights to borrow from this literature. For example, previous simulations and experimental work (Limanowski et al., 2018; Parees et al., 2014) have shown that a failure of sensory attenuation can lead to pathological alterations in self-generated actions – for example, the deficits in motor control seen in Parkinson's disease. In the immune analogue of pregnancy, a failure of 'sensory' attenuation could result in miscarriage or pre-eclampsia (Laresgoiti-Servitje et al., 2010). This could again be explored using a generative model (and its inversion) similar to that in Figure 1 by, for example, adjusting parameters of the prior or likelihood such that the concentration of Th1 cells (which produce pro-inflammatory molecules)[24] declines (or fails to do so). One manipulation that might achieve this is to attenuate the precision of the (likelihood) mapping from pathogens to MHC-I antigen presentation. Under the belief that the latter is not necessarily a consequence of the former (a valid belief in the context of pregnancy), one would expect a smaller update in beliefs about pathogens on observing MHC-I antigen presentation. If Th1 cell concentration embodies some aspect of this belief, this implies a smaller increase in this population of cells in response to MHCI.

[24] The ratio between the two types of T-helper cells (Th1 and Th2) is altered during pregnancy. A skew towards Th2 cells (which produce anti-inflammatory molecules) has been implicated in maintenance of healthy pregnancies, while a skew towards Th1 has been associated with recurrent miscarriages (Makhseed et al., 2001).

Neuroendocrine regulation of immunity

The above outlines insights that may be gained by applying theoretical neurobiological methods to the functioning of the innate and adaptive immune systems. However, my primary interest is in the interface between these systems and the brain. Elements of this interface are direct, but much of the interaction is via the hypothalamic-pituitary-adrenal (HPA) axis. Briefly, the hypothalamus synthesises corticotrophin-releasing hormone (CRH) that stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH). This acts upon the adrenal gland to stimulate cortisol release. In addition to suppressing further ACTH and CRH release, cortisol suppresses activity of Th1-cells and macrophages. In fact, corticosteroids are frequently used in clinical practice to suppress inflammation (Cole & Schumacher, 2005; Gegel et al., 2019). In turn IL-1, IL-6, and tumour necrosis factor (TNF) released by these cells normally increase hypothalamic release of CRH. Interestingly, CRH receptors are also found in the hippocampus, amygdala, and locus coeruleus (Herman et al., 2016).

In addition to the HPA axis, the hypothalamus directs immune responses through the autonomic nervous system. The sympathetic branch of this innervates lymph nodes directly (Kenney & Ganta, 2014). The hypothalamus also directly orchestrates the fever response to infection. As such, the hypothalamus may be seen as an interface between the immune system and the central nervous system. The importance of this role has been demonstrated in empirical studies (Alaniz et al., 1999; Barrios-Payán et al., 2016) and has been central to developments in theoretical immunology (Rosas-Ballina & Tracey, 2009; Tracey, 2009). This is important because, if there are physiological interfaces between the immune system and the brain, then these systems can be understood as jointly optimising a shared generative model (i.e., a Markov blanket can be drawn around both of them). Figure 3 depicts the HPA axis as a (simplified) example of the message passing that might emerge from inversion of a shared generative model between the immune system and the brain.

Neuroimmunological diaschisis

Typically, the interaction between the brain and the immune system is studied by treating the two as separate systems and asking how the immune system might attack the nervous system. The advantage of framing the nervous and immune systems as a *single* system – that solves a single generative model – is that it offers the opportunity to think about a neuroimmunological 'diaschisis'. A diaschisis (literally, 'shocked throughout') is a functional change in distant parts of a system following a localised lesion (Carrera & Tononi, 2014; Finger et al., 2004; Fornito et al., 2015; Price et al., 2001). The classical example of this is hypometabolism of the contralateral cerebellum following a motor-cortical lesion (von Monakow, 1914).

As an example of such a shared generative model, Figure 3 presents an interpretation of the neuroendocrine interface with the immune system in terms of a predictive coding-style message passing architecture. This is the sort of message passing that arises from writing down a specific kind of generative model. The implicit model in question here is inspired by models used to account for precision estimation (Kanai et al., 2015). Intuitively, one can think of this as prediction of some observable (from the perspective of the immune system) characteristic of a pathogenic population (e.g., its concentration), represented by the variable y. This prediction has two parts: (i) the expected concentration of that population (given by μ_x) and (ii) the variance expected around that expectation (given by $\exp(\mu_v)$). The implication is that the HPA axis and its relationship with the immune system can be accounted for by assuming a generative model in which Th1-lymphocytes predict the concentration of some pathogen, and cortisol represents a prediction about the uncertainty of that prediction. The negative feedback loops, characteristic of these systems, then emerge from the message passing used to update these Bayesian beliefs.

The idea here is that abnormal neural computation could arise from an immune lesion, because the (otherwise healthy) signalling from immune cells to neural tissue is altered. Similarly, psychiatric or

neurological insults might lead to abnormal neural regulation of immunity. We can see how this could work in Figure 3, noting the presence of CRH receptors in multiple brain regions. A polymorphism in a gene encoding a receptor in the immune system (e.g., the Th1 IL-12 receptor) might lead to changes in the release of cytokines by macrophages, changing the values of the variables represented in the hypothalamus. This changes the information available to other parts of the brain that respond to CRH. Note that this does not involve the immune system attacking the nervous system – the latter may respond optimally based upon the information available to it.

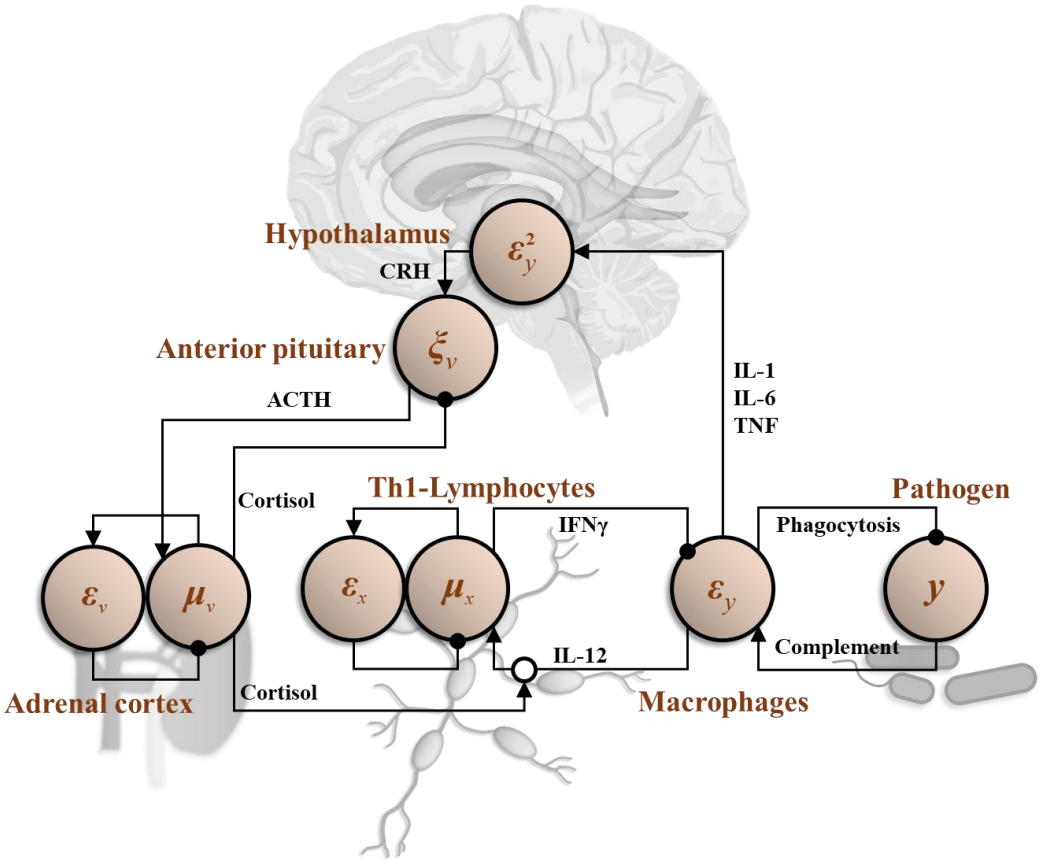

Figure 3. Neuroendocrine regulation of immunity via the Hypothalamic-Pituitary-Adrenal axis. This graphic shows the predicted pathogen concentration signalled by IFNγ derived from Th1-lymphocytes. This is subtracted from the complement pathway activation (playing the role of sensory data) detected by macrophages to give a prediction error (ε_y) represented by the IL-12 levels released by macrophages. Intuitively, the presence of unanticipated pathogens prompts an increase in macrophage activation. This prediction error may be resolved in two ways. The first is to decrease the amount of pathogen through phagocytosis and oxidative killing. The second is to increase the Th1 response (μ_x) to update predictions (IFNγ) so that they are consistent with the presence of pathogen. The degree to which the Th1 response is increased depends upon two things. The first is prior beliefs about the amount of pathogen expected. Deviation from this prior is indicated by the prediction error (ε_x), which may be intrinsic to T-cell populations. The second is the precision or inverse variance associated with the predicted pathogen concentration. If the variance is assumed to be very high, the effect of the prediction error (ε_y) on the expectation (μ_x) is attenuated. Here, I have assumed the expected variance is a function of some variable v whose expectation (μ_v) is signalled by cortisol from the adrenal cortex. This means that, when cortisol is high, the Th1 response to macrophage-derived cytokines is more limited. To update beliefs about variance, deviations from a prior value can be penalised as before (ε_v), but the prediction error from y has to be handled more carefully. As variance is a second order statistic (the expectation of a squared quantity), the prediction error needs to be squared (as shown in the hypothalamus) and compared to the current estimate of the variance. These (respectively) account for the cytokines released by macrophages and detected by the hypothalamus, and for the negative feedback from the adrenal cortex to the anterior pituitary – shown as the point at which the square prediction error and variance are compared (with ξ_v representing their ratio).

A diaschisis of vigilance?

Learning to appropriately infer threat is an essential and highly conserved facet of biological systems (Bach et al., 2018; Ojala & Bach, 2020). It is of great importance that these inferences be accurate[25]. Too much avoidance (or hypersensitivity) excessively and unnecessarily limits the interactions between the system and its environment, effectively starving it of (epistemic) resources; too little avoidance (hyposensitivity, or naïveté) can unnecessarily expose the system to risk. The brain and the immune system can certainly be seen as engaged in avoiding threats to their own integrity and that of the organism as a whole. 'Hypersensitivity' is a usefully intuitive term here, as it generalises well. Disproportionate and misdirected activity of the immune system is often a result of disorders collectively called hypersensitivities. These include allergies and autoimmune disorders, when the system mistakenly perceives its own tissues as threatening. Such conditions may result from, for example, variation of genes related to immunity, or environmental sensitisation. A number of central symptoms of psychiatric disorders can also be understood as hypersensitivities – such as social threat hypersensitivity in borderline personality disorder and depression (Badcock et al., 2017; Bertsch et al., 2013; Slavich & Irwin, 2014) or sensory hypersensitivities in autism (Takarae et al., 2016). There are several well-established links between hypersensitivities and psychiatric disorders; for example, systemic lupus erythematosus (SLE) and depression (Moustafa et al., 2020); thyroiditis and anxiety (Siegmann et al., 2018); SLE, psoriasis, rheumatoid arthritis and schizophrenia (Chen et al., 2019; Tiosano et al., 2017; Ungprasert et al., 2019). Indeed, some accounts even suggest that schizophrenia *is* an autoimmune disorder (Adams et al., 2012; Knight et al., 1992).

[25] Under the free energy principle, a fundamental drive for me, as a self-organising system, is to maximise the accuracy of my predictions about the causes of my sensations, with models of the world that are as minimally complex as possible – in order to maximise evidence for my own existence. The human brain and immune system are two of the most complex systems in biology, which speaks to the evolutionary imperative for them to be impeccably accurate in their predictions.

Through the lens of neuroimmunological diaschisis, an interesting question may be raised here. Under the hierarchical perspective of active inference, the brain and the immune system are internal states of the same Markov blanket and necessarily influence each other (Kirchhoff et al., 2018; Palacios et al., 2020). If one process (e.g., the immune response) within a larger Markov blanket is faced with a threat to its integrity, are other processes (e.g., psychological aversion) within that blanket primed towards threat avoidance as a result? If this is the case, an important story could be told about how and why immune insults – especially early in life or *in utero* – are linked to the manifestation of psychiatric disorders even decades later (Guma et al., 2019), and why people with certain psychiatric disorders are more likely to have allergies, autoimmune conditions, and to suffer from other hypersensitivities (Benros et al., 2014; Benros et al., 2011; Benros et al., 2013). Computationally, for this to be true, there must be a possibility of generalisation of prior beliefs about threat (and their precisions), both between concepts and across physiological systems within a Markov blanket. There is evidence from theoretical and behavioural work demonstrating the generalisation of prior beliefs and precisions across conditions (Fernandes et al., 2014; Kawashima & Kusnecov, 2002). I plan to expand on this notion in future work by considering whether there is an optimum degree of generalisation of threat avoidance between physiological systems.

A well-established model of threat learning in mammals is Pavlovian fear conditioning (Bach et al., 2018; Ojala & Bach, 2020), in which a neutral ('conditioned') stimulus is paired with a threatening ('unconditioned') stimulus such that an association is developed between the two. The result is that the neutral stimulus eventually engenders an aversive response even without the presence of the unconditioned stimulus. Experiments that lesion threat memory are challenging to conduct in human populations. In the next section, to illustrate the benefits of taking a theoretical approach, I outline an example of an *in silico* experiment that offers the opportunity to explore the effects of lesioning threat memory.

Simulation

Wet lab-based work that usually advances immunology is often expensive and time-consuming and clinical studies of immune and neurological disorders are usually faced with ethical restrictions. A major advantage of this kind of theoretical approach is in providing a proof principle that validates the various costs of pursuing a new hypothesis empirically. Translated into a generative model, an experiment can be simulated *in silico* with the requisite flexibility to define specific experimental and environmental parameters, which generate data. Or, trained on existing empirical data, it is possible to generate sophisticated predictions about outcomes given new data. For example, in recent work, we have used a similar modelling approach to investigate susceptibility to symptoms of, and likelihood of testing positive for, Covid-19 (Parr et al., 2020).

While this (conceptual) chapter is not the place for introducing new mathematical models or simulations, it is useful to think about how one would construct a generative model from which simulations could be developed. A challenge often faced by computational biology is the combinatorial complexity that cannot but be simplified for the purposes of simulation: biology is as messy as physics is neat. The advantage of the active inference approach is that if one can define the problem the system is solving, the Bayes optimal solution to this problem automatically tells us what the relevant (internal state) dynamics are. This lets us take a more focused, teleological and 'top-down' approach to understanding the neuroimmunological system, as opposed to trying to build up a model by writing down the dynamics of each component of the system and hoping for an emergent pattern.

In neurobiology, we typically start by selecting an experimental paradigm that involves presenting participants with some problem (sensory discrimination, decision-making, etc) that we know the brain can solve. To be able to solve such problems implies the brain's model of the world accurately accounts for how we (as experimenters) have generated the stimuli that were presented to the participants. Formalising this and computing the optimal solution tells us about the structure of that solution. This

typically involves a network of beliefs, with messages passed along the links of that network like action potentials along axons in a brain. This means there is no need to attempt to model the entire brain, and instead can focus upon the minimal networks required to explain the phenomena of interest.

Here, I consider the same construct, applied to networks that include message passing among elements of the immune system. The key challenge here is to identify the right sort of experimental paradigm, and to think about how that might be represented as a generative model. I illustrate the principles of this in relation to an existing experiment that demonstrates a neuroimmunological diaschisis. This is based upon a taste-aversion classical (Pavlovian) conditioning paradigm (Ader & Cohen, 1975; Ader & Cohen, 1991), in which rats were first injected with an immunosuppressant called cyclophosphamide (the unconditioned stimulus), or a placebo, and simultaneously fed either a saccharin-flavoured drinking solution (the conditioned stimulus) or plain water. This meant there were three groups. Group 1 were given saccharin and cyclophosphamide, group 2 were given plain water and cyclophosphamide, and group 3 were given plain water and a placebo. They were then injected with sheep red blood cells (i.e., foreign material that would typically induce an immune response). Three days later, some of the mice were re-exposed to saccharin. Ader and Cohen (1991) found that conditioned (cyclophosphamide-treated) rats showed a heightened aversion to saccharin (intuitively, this is similar to the human experience of an acquired aversion to foods consumed just before a period of illness); as well as, interestingly, a reduced immune response to sheep blood cells compared to placebo-treated rats and treated rats not re-exposed to saccharin.

Figure 3 illustrates the way in which this experimental design could be represented as a generative model. In addition, it shows the message passing scheme which could invert a model of this sort. The key features are the division into two streams (left and right) that deal with inferences about whether or not ‘I am infected’, and about the (gustatory) context. The former relies upon the (immunoceptive) detection of antigens, while the latter relies upon the presence or absence of saccharin (involving the

central nervous system). Despite this division between the two streams, this scheme models neuronal modulation of gain (precision) of the immune response. Classical conditioning can thus be understood as the process of learning about the temporal and/or causal relationships between external and internal stimuli. The value of formulating a model in this way is threefold. First, as alluded to above, it lets us select the minimal set of nodes in a message passing scheme that is needed in order to explain some facet of behaviour in an otherwise very complex system. Second, it gives us some intuition as to what the neuroimmunological system is 'trying to do', in the sense that the dynamics are now seen as solving an inference problem. Finally, it is consistent with the kinds of formulation used in computational neuroscience, enabling development of simulations for synthetic experimentation.

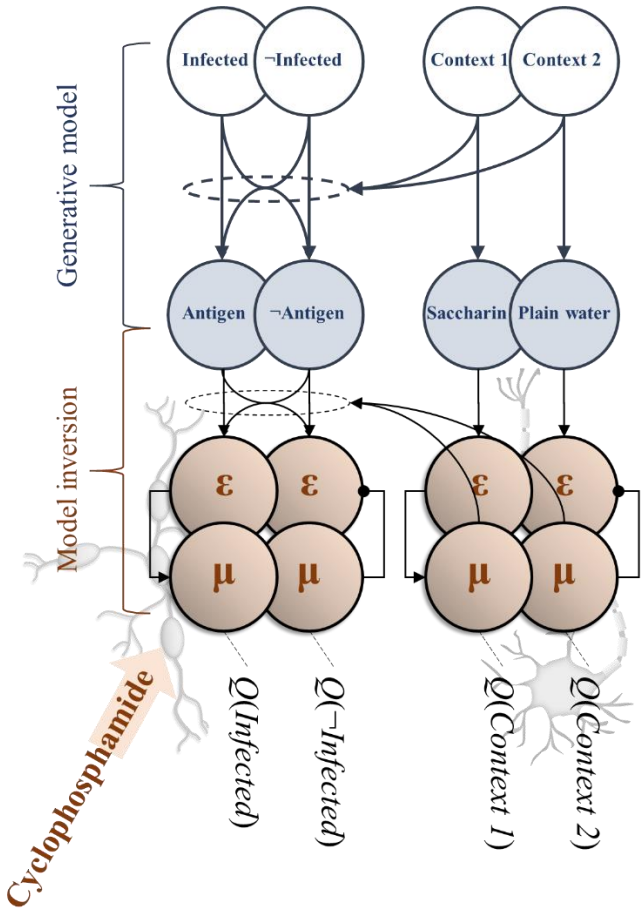

Figure 3. Classical conditioning of the immune system. This figure is a graphical representation of the classic taste aversion experiment by Ader and Cohen (1991). Here, the unfilled circles at the top represent the hidden states of the generative model (the saccharine-context for the nervous system and the presence of infection for the immune system). The filled blue circles represent sensory states or 'observations' (e.g., MHC-I presentation of sheep red blood cell antigens). The ε and μ symbols represent prediction errors and expectations (of a categorical sort) of the nervous (right) and immune (left) systems, which encode probabilistic beliefs (Q) about the hidden states. Cyclophosphamide treatment (unconditioned stimulus) suppresses the immune response, which precludes an 'infected' inference in the presence of antigen. This could be interpreted as attenuating the precision with which antigens are predicted (allowing for some probability of detection in the non-infected condition, and for some probability of non-detection in the infected condition). If this happens in the presence of saccharin only, this attenuated precision may be learned in a context specific way. Eventually, the presence of saccharin (conditioned stimulus), leading to an inference of 'context 1' implies low precision in the immune modality, and an attenuated immune response even in the presence of antigen.

Conclusions

In this chapter, I have introduced 'immunoceptive inference': active inference from the perspective of the immune system. This is in a similar vein to the notion of 'interoceptive inference', which frames emotions as emerging from—or perhaps furnishing—predictions about the causes of visceral sensations. In brief, interoceptive inference claims the brain is continuously updating predictions about, and acting upon, the body it inhabits (Seth, 2013). In my formulation, the body itself (in this case, the immune system) is seen as furnishing predictions of—and acting upon—sensory input, informing 'beliefs' about whether an antigen belongs to the category of 'self' or 'nonself'.

In so doing, I have highlighted three practical contributions (translation, unification and simulation) of the active inference framework to answering and – crucially – redefining the question, "Why are psychiatric disorders and immune responses intertwined?" I suggested that it is inevitable that two systems within the same Markov blanket influence each other: the brain and the body together make predictions about exteroceptive, interoceptive, and immunoceptive input. To this end, I have proposed an example of a common generative model that the brain and immune system jointly optimise, treating molecular components of the immune system as sensory or active states and the resulting cellular response as message passing at lower levels of a 'sensory' hierarchy that interfaces with the brain. This scheme expresses the classical conditioning of the immune system in terms of inference at an immunological level, that may alter the message passing at a psychological level (or vice versa) through an optimal interface between the two systems.

This surrender of mind-body and brain-body dualisms may be of particular importance to psychiatric practice, where it encourages a holistic treatment of patients. For example, with an embodied perspective on the mind, a patient presenting with psychosis may be treated with reference to the mechanisms leading to this syndromic endpoint, whether that be schizophrenia (treated with antipsychotics), or an alternative (e.g., endocrine) diagnosis such as Cushing's syndrome, which can be

effectively treated by normalising cortisol levels (Tang et al., 2013; Wu et al., 2016) – or indeed autoimmune encephalitis (Symmonds et al., 2018). I also advance the possibility of drawing immunological analogues of concepts defined under active inference for neurological phenomena, such as sensory attenuation. Finally, I introduce the novel concept of neuroimmunological diaschisis and the possibility of a diaschisis of threat-avoidance that may contribute to the overlap between psychiatric disorders and immunological hypersensitivities. This kind of overlap leads to clear empirical predictions; for example, an association between psychopathology and (measurable) immunological responses, much in the same way that clinical tools such as the dexamethasone suppression test leverages the link between neuroendocrine function and stress or depression (Naughton et al., 2014).

Discussion

In this thesis, I have examined the dysconnection hypothesis of schizophrenia and attempted to find a place for the immune system in the implicit synaptopathy. In doing so, I have discovered genes (*FAM89A* and *ENGASE*) and pathways ('Abnormal Neurotransmitter Level'), whose expression influences the mismatch negativity (MMN). These discoveries offer a first step towards understanding what is happening in the brain at a molecular level when a prediction error is being minimised. I have also found that human induced pluripotent stem cell (hiPSC)-derived neural progenitor cells (NPCs) from people with schizophrenia show an attenuated transcriptional response to the pro-inflammatory cytokines IFNγ and IL-1β. This finding may speak to a deficit in activating compensatory mechanisms in the face of an immune challenge. Both the empirical findings implicate the modulation of synaptic gain control. This is a key determinant of the augmentation and attenuation of message passing in neuronal circuits: especially when formulated in terms of predictive coding and the implicit role of precision weighted prediction errors in (Bayesian) belief updating. In the final chapter, I proposed that the brain and the immune system *together* predict sensory information (such as infection), exemplifying a common generative model that the brain and immune system jointly optimise. An interesting fallout of this formulation is the possibility that there is 'sensory' attenuation in the immune system, perhaps exemplified by the suppression of the immune response required to maintain a healthy pregnancy.

The overarching aim of this work was to find connections between different aetiological accounts of psychosis; and indeed, a number of interesting connections have emerged. One aspect that stood out was the repeated emergence of genes and gene sets involved in regulating synaptic efficacy – both in association with the MMN and in the responses to cytokine exposure. As might be expected, the MMN (and, implicitly, the encoding of prediction errors) is particularly dependent on genes that influence neurotransmitter levels in synaptic clefts; as well as *ENGASE*, which may influence synaptic communication via post-transcriptional modifications of potassium channels. This serves to support the

notion that (the precision of) prediction errors are encoded in the brain at a molecular level by the modulation of synaptic gain control. The fact that MMN amplitude is so consistently attenuated in psychosis (including in my own sample) – now with some formal grounds for its classification as an endophenotype – further suggests that there is a dysregulation of an underlying neuromodulation in people with psychosis, as proposed by the dysconnection hypothesis.

In Chapter 2, in amongst the immune response-related pathways that were most differentially expressed in response to cytokine exposure, were three gene pathways related to synaptic activity: 'post-synaptic density' (which includes genes encoding NMDA-Rs, such as *GRIN1*, and PSD-95, which is involved in trafficking NMDA-Rs), as well as 'presynapse' and 'presynaptic activity', both of which include genes involved in vesicle formation. This indicates that the effects of cytokine exposure are mediated both by neurons generating messages as well as neurons that are receiving them. Most interestingly, these were among the top five (of 895) gene pathways that showed an attenuated response to treatment in schizophrenia lines compared to control lines. NPCs do not have synapses, so there are two plausible interpretations of this result. Either these genes have functions beyond synaptic regulation; or, as suggested by (Warre-Cornish et al., 2020), these early inflammatory insults persistently dysregulate these genes such that the trajectories of synapse formation and elimination are altered – and even more so in cells from donors genetically predisposed to schizophrenia. In other words, the latter would suggest that the addition of an inflammatory insult exacerbates the development of synaptic dysfunction. In part, this gene-environment interaction may be explained by the difference seen in expression of the IFNγ receptor gene (*IFNGR2*) in schizophrenia compared to control lines, which may single out this gene as a target for further study of allostatic load in schizophrenia. Additionally, the top two genes differentially expressed in schizophrenia lines compared to control lines in response to IFNγ (*NDUFA2* and *NDUFS3*) were mitochondrial complex I genes. This suggests that schizophrenia donor cells may be driven to

conserve energy in response to an infection, while healthy donor cells are able to expend more energy to restore health (Mueller et al., 2021).

The trend seen in the neurodevelopmental enrichment analyses of MMN-associated genes may indicate that the neuronal structures that are necessary for short-term plasticity (and thought to underwrite belief updating) are largely established during prenatal development. Alternatively, it may suggest that processes governing such plasticity become increasingly deprioritised into adulthood. It is also interesting to note that *FAM89A*, most significantly positively associated with MMN amplitude, is particularly expressed in the placenta and foetal brain (as well as being implicated in the immune response). What is clear from Chapter 2 is that, at this very early stage of development, there is already a difference in the way NPCs from people with schizophrenia respond to immune challenges. This is interesting, because it suggests that even at the earliest stages of embryonic neurodevelopment, the coping strategies used by these NPCs are suboptimal. If such early insults are influencing cell fate or synapse formation, there may be repercussions for the emergence of cortical hierarchies. Indeed, recent work has shown that hierarchical control systems collapse from the top down (i.e., 'higher' levels are sacrificed, and temporal depth is lost) under stress and that this collapse favours short-term coping strategies[26] (Goekoop & de Kleijn, 2021).

It would be interesting to further examine whether this is reflected in the development of hierarchical cortical architecture in the presence of acutely challenging environmental (e.g., immune) influences at the earliest stages of neurodevelopment. For example, Warre-Cornish et al. (2020) showed a priming effect of cytokine exposure at the NPC stage that altered the transcriptional response further down the line when they had formed neurons (with synapses). It has also been shown that the gene expression patterns of individual NPCs determine their differentiation and migration to specific cortical

[26] In this Bayesian control systems account, stress is synonymous with prediction error.

laminae – and ultimately, therefore, the formation of cortical hierarchies (Nowakowski et al., 2017). If there is an impact of immune priming on the differentiation of NPCs, this would certainly be of significance in explaining why there may be failures of handling of prediction errors in psychosis. It may be interesting in future work to grow immunologically 'primed' NPCs further into organoids and (using single-cell RNA sequencing) assess whether cortical hierarchies may be emerging differently after priming.

In Chapter 3, I pursued the theme of message passing and belief updating in the extended immune system through demonstrating a computational approach to neuroimmunology, which has a variety of potential implications. First, the benefit of an inferential approach to the immune system – to my knowledge, new to the immunology literature – offers a new avenue for posing questions about how the immune system differentiates 'self' from 'other' (Kitamura, 2008). Secondly, how, in a healthy pregnancy, the mother's immune system does not reject the foetus is a major open question. When the delicate balance of this maternal-foetal tolerance is tipped, the repercussions can include pre-eclampsia and miscarriage. To see pregnancy as 'sensory' attenuation in the immune system is quite a radically different perspective of both sensory attenuation and pregnancy. The philosophical implications here are significant, adding to the argument against mind-body and brain-body "crypto-Cartesian" dualisms (Nachev, 2011) from a field (immunology) often alien to contemporary philosophical literature. This sort of rejection of dualism for an 'embodied' mind perspective of the brain has implications for a holistic treatment of patients with psychiatric disorders. For example, with an embodied perspective on the mind, a patient presenting with psychosis is more likely to be treated with reference to the mechanisms leading to this syndromic endpoint, whether that be schizophrenia (treated with antipsychotics, which come with major side-effects), or an alternative diagnosis such as Cushing's syndrome, which can be effectively treated by normalising cortisol levels.

The possibility of simulating the immune response allows us to non-invasively manipulate variables such as MHC-I presentation and observe their impact on this balance. Furnishing these simulations with empirical data (i.e., training the models) could also give us a powerful predictive model of the viability of a pregnancy (for example, the likelihood of a preterm delivery or a rhesus pregnancy given maternal antibody titres and obstetric history). Indeed, I plan to use this formulation to build a clinical tool for this purpose in future work, as a precision medicine approach to identifying a need to take preventive measures (e.g., planned Caesarean section or alteration of specific lifestyle factors). We similarly present a shared generative model between the brain and the immune system, which offers a formal approach to understanding the functional dysconnections that may underwrite systems-level changes (or 'neuroimmunological diaschisis') that results from disturbing one part of an interconnected network of 'belief' updating.

There are some limitations of the work presented and future directions that reasonably follow. In Chapter 1, due to the nature of our phenotype, which is rarely obtained in combination with genetics, our sample size was rather limited. This created a ripple effect of compromise that had to be made in several aspects of the analyses. For example, sample size and power were important considerations in selecting our tissues of interest: I had to balance the power of the PrediXcan tissue models against the power of our own sample. I felt the best decision would be to choose only the tissues that best account for the functional anatomy of the phenotype, as our findings would have been excessively noisy if we were to include other tissues that were of less relevance. The two tissues included (frontal cortex and whole cortex) were therefore chosen for their relevance to the phenotype: the functional anatomy of MMN is well studied and it is established in the literature that MMN engages the inferior frontal gyrus and superior temporal gyrus (Doeller et al., 2003; Opitz et al., 2002) The frontal cortex encompasses the inferior frontal gyrus, and we included the whole cortex to account for the superior temporal gyrus.

However, it would have been ideal to assess a wider range of tissues – especially 'Whole Blood', which accounts for more genes than either of the tissues we studied.

Another issue due the small sample size in this study was that the standard errors of the heritability and genetic correlation estimates used for calculating the Endophenotype Ranking Value (ERV) were large. Additionally, as ERV is a recent development in the field, there is limited precedent upon which to specify a minimum sample size for meaningful results. The original paper which proposed ERV as a formal approach to the identification of endophenotypes (Glahn et al., 2012) used 1222 individuals to calculate family-based heritability of endophenotypes and their genetic correlation with disease liability. Family-based heritability estimates tend to be higher than purely SNP-based heritability estimates – otherwise known as the 'missing heritability' problem (Maher, 2008; Yang et al., 2017). As a result, our sample size of 728 was likely short of what would have been necessary to make conclusive claims. In the absence of a wide body of previous literature using ERV, there were three factors I considered to be of importance: 1) the heritability of the endophenotype; 2) the heritability of the disease; and 3) the novelty of the findings. The latter is important because it has not been possible before to formally assess the utility of MMN as an endophenotype for psychosis, although it is one of the most likely candidates thereof. The first two are important as the ERV is directly derived from these measures. Stanton-Geddes et al. (2013) suggest that, with samples drawn from relatively well-controlled environments, sample sizes of a few hundred can yield meaningful SNP-based heritability estimates). The ERV presented here for MMN therefore represents, at most, a principled starting point for gauging the value of MMN as a psychosis endophenotype.

Furthermore, in order to assemble a large enough dataset for a genetic association study, we also had to compromise on the homogeneity of the samples: I combined samples that used slightly different MMN paradigms. I attempted to account for these differences in methodology by combining the samples by

meta-analysis, as well as by including testing centre as a covariate in the regression analyses. However, future studies would ideally use a larger and homogenously tested sample.

Another limitation here was that relatives of patients with psychosis were grouped with healthy controls. This was based on a regression analysis which showed no significant difference in MMN amplitude between relatives and controls. However, it could be argued that as the relatives of patients with schizophrenia are likely to be more genetically similar to people with schizophrenia than non-related healthy controls would be, they should be analysed as a separate group. Indeed, other studies, such as Bramon et al. (2004), have taken this approach. This was yet another compromise we made due to sample size, as the number of relatives in our sample (n = 84) was too underpowered to consider them as a separate group.

It was also somewhat challenging to interpret the main finding from Chapter 1 (the association of *FAM89A* and *ENGASE* with the MMN) mechanistically, as there is very little known about these two genes as yet. Future work, perhaps using knock-out mouse models, would be invaluable in investigating the functions of FAM89A and ENGASE and for hypothesis-based testing of their influence on the MMN.

In Chapter 2, the sample size was perhaps an even greater concern: case-control comparisons of gene expression within a sample size of six cannot be considered reliable without replication. In large part, this is because culturing iPSC-derived neural progenitors remains expensive, rare and time-consuming. Indeed, this is a limitation faced by most studies that use this technique to date, with even the largest studies using hiPSC-derived schizophrenia NPCs or neurons having no more than fourteen lines in each group (Brennand et al., 2015; Hoffman et al., 2017). Of our findings, those most likely to be reliable are the treatment versus vehicle comparisons, as these were experimentally manipulated, acute – such that the induced response involved thousands of genes – and consistent with previous literature (the top pathways that were observed were canonical IFNγ and IL-1β signalling pathways). Nevertheless, statistically, it is difficult to say whether or not these findings can be accepted: this remains inconclusive

in the absence of further validation. I think the main value of these experiments are, once again, their novelty: they take a first step towards understanding the effects of these cytokines on neuronal networks and their roles in the aetiology of schizophrenia, providing a frame of reference for future studies.

A major limitation in Chapter 2 is that polygenic risk scores (PRSs) were not available for all of the NPC lines in the DGE experiments. We defined the groups in our study (cases and controls) by the diagnosis of the adult donors. However, in theory, one could say that PRS is a better determinant of the case-control status of NPCs in the absence of epigenetic modifications, which are almost entirely eliminated by reprogramming of primary keratinocytes into iPSCs. This particularly comes to the fore as a limitation because of the two participants with schizophrenia for whom PRSs were available: one of these had a high PRS (with low cannabis use), while the other had a low PRS (with high cannabis use). Again, with the removal of epigenetic modifications by reprogramming, the schizophrenia-related genetic profile of the hiPSC-NPCs is perhaps the best determinant of whether a cell line should be labelled as 'case' or 'control'. Some mitigation is provided by the fact that our principal component analysis does show stratification by diagnostic group; and at present, PRS for schizophrenia is still to be developed to a sufficient degree of predictive validity (Curtis, 2018; Janssens, 2019). These findings would be more reliable, nevertheless, with support from a replication study which calculates polygenic risk scores for all lines and compares results when stratification is done by donor diagnosis as versus PRS.

With regard to Chapter 3, it would be important to note that the active inference framework has not been universally adopted by researchers in the field of computational psychiatry. The foundations of active inference lie in seasoned concepts such as variational Bayesian mechanics and Helmholtzian inference, but the intricacies and applications are continuously expanding. The literature in this field is therefore rather as dynamic as that which it describes. As a result, there are some ongoing debates about mathematical details and philosophical interpretations (Andrews, 2020; Biehl et al., 2020; Bruineberg et

al., 2020; Friston et al., 2021). There are, for example, philosophical disputes around the fringes as to whether the generative model of an organism is a representation, like a map (i.e., something the organism 'has'), or a description of phenotypic dynamics that underwrite the organism's existence (i.e., something the organism 'is') (Constant et al., 2020).

The same could be said about the dysconnection hypothesis of schizophrenia. The literature on the aetiology of schizophrenia is also highly dynamic and consists of several disparate strands from different disciplines, as laid out in the general introduction. Indeed, fostering greater coherence between these bodies of literature was one of the main objectives of the work in this thesis. As a result, different areas of neuroscience seem to lean towards different hypotheses of schizophrenia – likely due to the history of the field more than as a conscious stance. In other words, not every researcher studying schizophrenia is likely to be familiar with the dysconnection hypothesis. Indeed, until now, there has been little crossover between the dysconnection hypothesis and immunology.

In summary, this thesis has laid important groundwork for developing a clearer picture of the neurobiological mechanisms that result in the phenomenon of the mismatch negativity and its attenuation in psychosis. These findings implicate *FAM89A* and *ENGASE* as key components of the physiology of prediction error minimisation. Further, I have found that there are differences in how the brains of people with schizophrenia may have responded to infection or inflammation during prenatal development. I suggest that immune insults early in life can alter neurotransmission, identifying new gene targets for future research on the influence of maternal immune activation on schizophrenia susceptibility and resilience. Taken together, this work provides support for the dysconnection hypothesis of schizophrenia and suggests mechanisms by which prenatal immune activation confers an allostatic load that elicits or exacerbates the synaptopathies that underlie psychosis.

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